Helicobacter pylori Infection in Children: An Uphill Climb

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Helicobacter pylori (H. pylori) is a worldwide infection and is common in children. Childhood is a crucial stage of life for *H. pylori* infection because this is when the infection is most commonly picked up. The infection seems to be running in families, also it is transmitted through contaminated water supplies. Once the infection is acquired it almost becomes a chronic infection. The prevalence is different from country to another, and it is more in the developing countries with low socioeconomic levels. The pathogenesis of *H. pylori* induced diseases differ to some extension in children than in adults. The infection can be asymptomatic, and the symptoms could range from abdominal pain up to peptic ulcer disease. Also, the infection can present with extra gastrointestinal manifestations most commonly iron deficiency anemia and idiopathic thrombocytopenic purpura. Investigations for *H. pylori* include invasive and non-invasive methods and differ in availability and accuracy. There is argument about indications to investigate for and treat *H. pylori* in the pediatric population and there is mauls of antibiotics for *H. pylori* in general practice. The goal of this review is to concentrate on the prevalence of *H. pylori* in the pediatric population especially in developing world, indications for treatment and when to investigate for *H. pylori* according to the guidelines.

INTRODUCTION

Helicobacter pylori (H. pylori) is a helical, curved, gram-negative, microaerophilic bacteria. It has 3-7 sheathed flagella on which are responsible for the organism's motion and invasion activities **[1]**. For a chronic infection of the epithelium of gastric mucosa, H. pylori is specially adapted **[2]**. Bizzozero was likely the first person in nineteenth century that mentioned the occurrence of spiral microorganisms in the gut of animals **[2]**. Warren and Marshall cultured H. pylori from gastric tissue for the first time in 1982 **[3]**. Childhood is a crucial stage of life for H. pylori infection because this is when the infection is most commonly picked up. However, the effects of infection are delayed until later in life and are limited in the early years **[4]**. Children who have H. pylori infection differ from adults in that they rarely experience infection-related complications. Additionally, there are fewer treatment options and indications **[5]**.

As there is abuse in general practice in rushing for searching and treating the infection without being indicated, the goal of this review is to concentrate on indications of treatment and when to investigate for H. pylori.

METHODS OF TRANSMISSION

In general, H. pylori spreads most frequently from person to

person, especially within families, with mother to child transmission being the most common. Flushed gastric juice or vomitus can cause oral-to-oral transmission, which also occasionally happens through the gastro-oral and fecal-oral routes **[6].** Contaminated water can also serve as a source of infection. Additionally, food may help spread disease **[7].** It has been demonstrated through molecular fingerprinting that the same strain is passed down through families **[8].** Once the infection is acquired, it is believed to be a chronic, long-lasting infection **[9]** and spontaneous clearance is relatively uncommon **[9-11]**. However, there was no increase in prevalence by age in a research of kids where age based prevalence was measured every year **[12]**. This indicates that children can contract transient H. pylori infections **[9, 13, 14]**.

PREVELENCE OF H. PYLORI

H. pylori infection is widespread worldwide and can either be symptomatic or asymptomatic. Due to better living conditions, socioeconomic advancement, and sanitation, the frequency of H. pylori infection among adults and children has been declining in the developed world in recent years. However, the developing world continues to have a high prevalence of it **[15]**. In Egypt**,** a study done in among apparently healthy school children in Al Qulubia governorate using serum IgG against H. pylori, the prevalence found to be 44% **[16].** Differences in prevalence of H. pylori worldwide are shown in **Table 1.**

PATHOGENESIS AND VIRULENCE FACTORS

H. pylori is a Gram-negative flagellated bacterium. It is a member of genetic populations with a wide genetic diversity **[18, 19]**. Despite the fact that H. pylori stimulates adaptive and innate immunity, these defenses are insufficient to stop the infection, that could last for years without treatment **[20]**. Low oxygen concentrations are not a problem for the organism. According to the physiological action needed, such as viability during difficult environmental conditions (pH or temperature shifts, gaps through meals, and treatment with antibiotics), it can switch between two shapes **[21]**. The organism can appear as a rod even though it typically has a spiral shape. Additionally, the coccoid shapes may manifest while in long in vitro culture or antibiotic treatment **[22]**. One of the ways that this bacterium survives in the host's gastrointestinal tract (GIT) is through its capacity to switch from spiral to coccoid form **[23, 24]**.

H. pylori move in the direction of the gastric epithelium and pierce the mucus layer using flagella-mediated motility **[25]**. The organism then moves from the acidic field to places with the right position. The coccoid form made it possible for it to colonize the mucus layers **[24, 26]**. The production of adhesin is how it attach to host epithelial cells attach **[25, 27].** Numerous studies have so far demonstrated that H. pylori colonization may be both negatively and favorably related to the onset and development of a number of diseases **[24, 28-32]**. It has been connected to duodenal ulcers (DU),gastric ulcers (GU), cancer stomach, and stomach mucosa-associated lymphoid tissue (MALT) lymphoma **[30, 33, 34]**. In order to survive at a lower pH, it has developed some virulence factors as one of its adaptation mechanisms. The bacterium can use the urease enzyme to neutralize stomach acid **[26]**.

Up till now, the exact pathogenesis of H. pylori in gastric and other diseases remains arguable **[35]**. It depends on the strain of bacteria. However, multiple other factors have an effect. The possession of a particular virulence factor is responsible for the interaction between the host and the bacterium **[36]**.

Effect on immunity and gastrointestinal microbiota: Innidiation of H. pylori causes an inflammatory reaction in the mucosa of the stomach; that is defined by the increase of production of cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor alpha (TNF-), and is mediated by neutrophils and mononuclear cells **[37]**. These cytokines produce reactive oxygen species (ROS) in the gastric mucosa **[38]**. Gastric mucosal injury results from ROS damaging vital biomolecules like DNA, lipids, and proteins during the inflammatory response. On the other hand, ROS also cause the production of the cytotoxic molecule malondialdehyde (MDA) **[39]**. Nitric oxide (NO) and prostaglandin E2 are upregulated in conjunction with this inflammatory response and are brought on by the increased expression of NO synthase and cyclooxygenase-2 (COX-2) **[40]**.

Chronic H. pylori infection alters gastric acid secretion, which may have an impact on both children and adults' gastric microbiota **[41-43]**. According to several reports, H. pylori has a major effect on the bowel microbiota **[43]**.

Previous research on the gastric microbiome revealed that H. pylori-related diseases may be greatly influenced by the interactions between H. pylori and other microbes **[41, 44-46]**. majority of the gastric microbiome in the general population. Between those who had H. pylori infection and those who didn't have, there were Proteobacteria, Bacteroidetes, Firmicutes, and Actinobacteria are the four phyla that make up the

startling variations in the composition of the gastric microbiome **[46, 47]**.

Table. 1: Frequency of H. pylori infection worldwide **[16, 17].**

Site of the study	Age group	Method of detection	Results	Authors
Egypt	6 to 13 years old children	IgG by ELISA	44% (176/400)	Mohsen M. Deeb, Dalia H. Abou-Elela, Wael A. Bahbah,Marwa M. Hessen
Norway	Kids 0 to 11 years, teenagers 12 to 17 years and adults above age of 18 years	SAT	Almost undetectable (0.6%) in all age groups, 20% in teenagers and about 45% in the adults	Paulssen E.J, Breckan R.K, Asfeldt A.M, Florholmen J, Kvamme J.M, Straume B
Poland	children aged 1.5 to 18 years	Upper endoscopic biopsy and culture	16.05% positive, the greatest prevalence was (23.06%), recorded in the year 2000, while the least was (8.90%) in 2010	Biernat M.M, Bińkowska A, Iwańczak B, Grabińska J, Gościniak G
China	Children from 3 to 18 years	^{13}C UBT	overall prevalence was 18.6%, rise with age (14.8% in 3 to 6, 20.2% in 7 to 11 and 25.8% in 12 to 17 years old) while it declines with time (in 2007 was 21.6% and in 2014 was 17.2%)	Shu X, Ping M, Yin G, Jiang M
Iran	Whole population, adults, and kids	ELISA or H. pylori antigen in stool	pooled prevalence of infection between whole population, adults, and kids were 54%, 62% and 42% respectively	Moosazadeh M, Lankarani KB, Afshari M
Japan	13 to 15 years old, Another study done in students aged 12 to 15 years	ELISA and then a UBT	only 85 children (4.8%, 85/1,765), in the other study the overall prevalence was 3.1% (14/454)	Nakayama Y, Kusano C, Gotoda T, Hidaka H, Ishikawa H, Moriyama M Lin Y, Hongo M, Kikuchi S
Sub-Saharan Africa	Mean age was 10.5 ± 2.7 years	H. pylori antigen in stool	overall prevalence in this study was 14.2%.	Tuoyire D.A, Awuku Y.A, Alhassan I.K, Simpong D.L, Afaa T, Adu P
Mexican	Children aged 0 to 5 years	Oral swabs using PCR	21 of 162 samples (13%)	Castro-Muñoz LJ, Muñoz-Escobar A, González-Díaz C.A, Tovar-Ayona B.J, Vargas-Olmos R, Aguilar-Anguiano L.M,
Iceland	Kids from 7 to 9 years old and teenagers from 16 to 18 years old	ELISA	Overall, 3.4% (7/205)	Kjartansdottir I, Asgeirsdottir G, Olafsdottir A, Hrafnkelsson H, Hreinsson J, Johannsson E

ELISA: Enzyme-linked Immunosorbent Assay, **IgG:** Immunoglobulin G, **PCR:** Polymerase Chain Reaction, **SAT**: Stool Antigen Test, **UBT**: Urea Breath Test.

H. pylori cytotoxins:
Bacterial persistence in the stomach depends on two major toxins that are encrypted by the pathogenicity island (PAI) genetic locus: cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA). Numerous host cellular processes are known to be impacted by CagA and VacA in order for the pathogen to successfully establish itself **[48]**. Cag PAI encodes a number of proteins that make up the constitutional elements of the bacterial type IV secretion system (T4SS) in addition to CagA and VacA expression. While the cag PAI is absent in some H. Pylori strains, those that are cag PAI-positive cause epithelial cells to overproduce IL-8. People infected with cag PAI-positive strains experience peptic ulcer disease (PUD) and gastric malignancy more common than those had infection with cag PAI-negative strains **[49]**.

Difference between pathogenesis in adults and children: The strains that infect either children or adults differ only slightly from one another. The main recognized colonizing and pathogenic factors, such as Blood group antigen-binding adhesion (BabA), Sialic acid-binding adherence (SabA), cagPAI, VacA, and others, are the same. However, as people develop, the host response can vary between children and adults. Additionally, the expression of H. pylori virulence factors may alter in response to variations in the gastric conditions brought on by infection. The majority of environmental factors that can influence how an infection develops, like smoking, alcohol consumption, and using drugs, are largely absent in pediatrics, resulting in almost "pure" pathology in comparison to adults **[4]**.

In Chile, Harris and colleagues showed differences between the histopathology and T cell responses among 79 adults (65% infected) and 36 children under the age of 12 (50% of whom had H. pylori infection) **[50]**. They found fewer Polymorphonuclear leukocytes (PMNs) and mononuclear cell infiltrate and a healthy epithelium in pediatrics compared to adults. They were able to show that, compared to adults, both infected and uninfected children have significantly higher levels of T regulatory cells (Treg) and Treg cytokines, while adults have higher levels of interferon alpha (IFN-□) expression. Then, in comparison to adults, it seems that Treg activity in children reduces the inflammatory process, so the gastritis scores are less **[50]**.

Identical outcomes were collected by Freire de Melo and colleagues, they came to the conclusion that the children's higher vulnerability to infection and bacterial persistence can be due to decreased inflammatory response in the mucosa of the stomach **[51, 52]**.

Because of this, H. pylori infection cannot be completely cleared by pediatric patients' immune systems, and if left untreated, the bacterium remains in the gastric environment.

CLINICAL PRESENTATION

1. Gastrointestinal Manifestations

Children of school age frequently experience GIT complaints, and 25% of them experience severe abdominal pain that interferes with daily activities. Infection with H. pylori is believed to be almost asymptomatic in children, but also it is attributed to some of GIT symptoms. The most frequent correlation between infection with H. pylori and abdominal pain or vomiting is with the presence of PUD. H. pylori infection symptoms have also been linked to localized epigastric pain and nocturnal awakening **[53]**.

Gastritis
As previously mentioned in the pathogenesis, H. pylori innidiation causes an inflammation in the stomach mucosa. After the acute phase, it progresses to chronic gastritis, that is marked by the accumulation of lymphocytes or plasma cells, the development of lymphoid follicles, and the hyperplasia of cells that make up the gastric glands. It results in a lifelong inflammatory response that is persistently chronic and low intensity in the gastric and duodenal mucosa **[54]**.

Peptic ulcer (PU)
Epigastric pain, usually relieved by food or alkali, is the main symptom of PUD. H. pylori causes ulceration in the stomach and duodenal mucosa when it attacks metaplastic stomach epithelium because it is trophic for this type of epithelium **[55]**.

The degree and distribution of gastritis determine the location of a PU. Bile inhibits H. pylori, so it typically cannot infect the duodenum **[55]**. However, DU could occur if pH is chronically low enough in the duodenal bulb, facilitating the infection and swelling of the metaplastic stomach mucosa in the duodenal bulb as low pH precipitates bile salts **[55]**.

Gastritis tends to start out being the worst in the antrum and then advance proximally into the

fundus because H. pylori density and affection of the gastric mucosa are the largest in the non-acid producing part of the stomach (i.e., the antrum) **[56]**.

Marshall and Warren **[3]**linked H. pylori infection with PUD in 1983. Since then, it has been established that non-steroidal anti-inflammatory drugs (NSAID) and H. pylori are the two main causes of PUD **[57]**.

In children with symptoms who undergo endoscopy, H. pylori-related ulcers are uncommon. Only 3.5% of children under the age of 6, 4.6% of children aged 6 to 11 years, and 10.4% of children over the age of 11 years had gastric or duodenal ulcers, according to a European research involving 1322 kids that had H. pylori infection **[58]**.

Functional dyspepsia (FD)

In the developing and developed worlds, FD has a community prevalence of 1.8–3.5 percent and 5–10 percent, respectively. It is a common functional gastrointestinal disorder in children **[59, 60]**.

As regard Rome IV criteria, published in 2016, FD is the existence of one or more of these symptoms: early satiety, epigastric pain, fullness postprandial or epigastric burning. These symptoms must have been present for at least three months prior to diagnosis and their onset must have been at least six months prior to diagnosis **[61]**.

A subset of FD patients who receive H. pylori eradication treatment report improved dyspeptic symptoms, despite the fact that the method of affection of GIT pathophysiology by H. pylori is still unknown **[62-64]**. The Kyoto Global Consensus Meeting for H. pylori Infection, that took place in 2014, established that resolution of symptoms from 6 months to 1 year after effective elimination indicates that H. pylori is the reason for the symptoms and justifies classifying H. pylori-associated dyspepsia as a distinct clinical entity **[65]**. Rome IV also agrees with this idea **[61]**.

H. pylori and gastroesophageal reflux disease (GERD)

The relation between GERD and H. pylori remains debatable. A study done in Romania, included 72 children proven GERD by 24 pH monitoring, and 62 controls, there was non-significant difference between patients and controls in the Prescence of H. pylori as proved by biopsy (26% and 16 % respectively) **[66]**.

While another study in New York, involved 420 patients underwent upper endoscopy and biopsy, found that the prevalence of reflux esophagitis in the *H. pylori* positive population was 81.3% compared to 38.1% in the *H. pylori* negative population **[67]**.

In a Mongolian research, people with GERD were less infected with H. pylori (63.6%), in comparison to those with DU (100%), GU (90%) and atrophic gastritis (77%) **[68]**. According to an Iranian research, no discrepancy was found in the prevalence of H. pylori in patients with GERD in comparison to controls **[69]**.

Regarding laryngopharyngeal reflux disease, screening for H. pylori in specimens from tonsils taken from patients undergoing tonsillectomy in Lithuania was done. Compared to the control group, the chronic tonsillitis group had a noticeable greater incidence of infection (56.5%) while it was 31.4 % in the control. Adults and kids both came to the same conclusions. Oedema of the vocal cord, disseminated laryngeal edema, and posterior commissure hypertrophy were laryngopharyngeal reflux-related symptoms that were found to be significantly correlated with a positive H. pylori test **[70]**. However, pathogenesis of GERD with H. pylori infection still unknown, and GERD is not an indication to investigate for H. pylori.

2. Non-GIT manifestations:

A-Hematological disorders

Iron Deficiency Anemia (IDA)

Searching for H. pylori infection in pediatric population is advised in cases of refractory IDA because several studies have linked low iron status and H. pylori infection. Children's low iron stores are a result of their elevated growth-related iron needs. They most likely develop iron deficiency (ID) more quickly in the presence of infection than adults. Hypochlorhydria is a cause of ID in H. pylori-associated atrophy by altering the physiology of iron-complex absorption. In a prospective study involving 123 kids, Harris et al. **[71]** discovered that hypochlorhydria, infection with H. pylori as well as inflammation all play a part in the cause of ID.

Hepcidin, a small protein made in the liver that controls the body's iron balance and recycling, as well as enterocyte iron absorption and macrophage iron release, was the material of a study by Azab et al. **[72,73].** Serum value of hepcidin is elevated by H. pylori infection, that blunts the efficacy of iron therapy **[74]**. Other

potential reasons for IDA in people with H. pylori include GIT bleeding either chronic or acute brought on by erosive gastritis **[75-77]**. According to Hershko et al. **[78]**, after H. pylori was eradicated, IDA completely vanished in 64 percent to 75 percent of patients who had both IDA and H. pylori infections.
In cases of IDA, according to recommendations for treating H. pylori infection, the infection should be cleared up **[79]**.

Immune thrombocytopenic purpura (ITP)
An autoimmune condition known as ITP is characterized by the immune system destroying otherwise healthy platelets **[80]**. ITP secondary causes include the well-known H. pylori infection. ITP patients are more frequently infected with of H. pylori than healthy people of the same age and gender **[81]**.
In 1998, Gasbarrini et al **[82]** first noted an association when they discovered that ITP patients' platelet counts significantly increased after H. pylori removal.
Further supporting the causal relationship was a review of 11 controlled studies that revealed an improvement in the platelet count in 51% of patients with H. pylori infection as opposed to an increase in platelet count in 8.8% of H. pylori-negative controls **[83]**.
ITP caused by H. pylori has a good long-term prognosis, according to research. After successful eradication, no recurrence was observed in an 8-year follow-up study**[84]**.
Regarding the part played by H. pylori in the pathogenesis of ITP, no mechanism is established. Antibodies to the H. pylori CagA and platelet antigens are linked to molecular mimicry **[85]**.
In summary, the identification and eradication of H. pylori in ITP is supported by studies to date. Patients with H. pylori infection may benefit from eradication therapy, according to the most recent American Society of Hematology guidelines **[80]**. Additionally, as regarding the most recent European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines, chronic ITP is a sign that an infection with H pylori may exist and should be treated if it does.

Vitamin B12 deficiency
O'Connor first identified the connection of insufficiency of vitamin B12 with H. pylori infection in 1984. He found organisms look like campylobacter in patients that had pernicious anemia and type A gastritis **[86]**. Researches have shown a connection between persistent H. pylori infection and vitamin B12 malabsorption **[87]**. Another study revealed that 29 out of 43 patients with H. pylori infection had vitamin B12 deficiency (67.4% of them) **[88]**. However, there are insufficient interventional studies showing how anti-H. pylori therapy affects vitamin B12 deficiency **[89]**.

B- Effect on growth:
H. pylori has been linked to effects on growth metrics in young children. The conclusions of studies examining how H. pylori infection affects a child's growth have a wide range of variance. Numerous studies have connected H. pylori infection to a reduction in children's growth **[90-92]**. However, cross-sectional research from various nations indicates that there is no association **[93-96]**.
According to one mechanism, H. pylori reduces gastric acid secretion, which may lead to enteropathogenic infection, which may cause diarrhea, malabsorption of nutrients, decreased food intake due to dyspepsia, and iron-deficiency anemia **[97, 98]**. However, it is challenging to demonstrate that H. pylori alone causes childhood growth impairment in the presence of so many confounding factors, including socioeconomic status and diet **[99]**.

C- Effect of H. pylori on asthma and allergy:
Early H. pylori acquisition may protect against allergy and atopic diseases, according to previous epidemiological studies **[100]**. This relationship was examined in three studies, with varying conclusions. In a case-control study from Greece, stool antigen test (SAT) for H. Pylori results showed that 29.6% of kids without asthma had the infection, compared to 11% of asthmatic children (P =.026) **[101]**. Additionally, 274 patients aged 3-76 participated in an Istanbul cross-sectional study to estimate the prevalence of H. pylori among people that had allergic and nonallergic nasal disorders in comparison to controls. In the pediatric group, no connection was found between the infection with H. pylori and the prevalence of allergic disease **[102]**.

D- Long-term complications of H. pylori infection:
Long-lasting H. pylori infection is a Group 1 carcinogen with sufficient evidence to suggest that it can result in low-grade B-cell gastric

MALT lymphoma and non-cardia gastric carcinoma **[103]**.

DIAGNOSIS

ESPGHAN and NASPGHAN guidelines state that, unless certain conditions apply, pediatric patients should not be treated using a "test and treat" strategy, which involves using a noninvasive test instead of an upper GIT endoscopy to establish H. pylori infection **[104]**. Contrary to recommendations for adult populations, H. pylori testing is not advised for kids who present with functional abdominal pain **[104]**.

Indications to test for H. pylori in children:

Children that have first-degree relatives with gastric cancer are advised to be tested and treated **[104]**. The guidelines also suggest that after ruling out other potential causes, searching for H. pylori should be taken into consideration in kids with refractory IDA **[105]**.

According to the evidence currently available, therapy for H pylori eradication is not anticipated to alleviate symptoms in pediatric population, with the exception of PUD cases **[106]**. Consequently, invasive tests done for the only aim of detecting H pylori infection ought not to be carried out if peptic lesions are not probable clinically or not diagnosed with endoscopy.

Noninvasive testing should be used in the patient with chronic ITP to determine the possibility infection. If it is positive, it must be determined individually whether an upper endoscopy is required prior to eradication therapy depending on the platelet count **[100]**.

Methods of diagnosis

Invasive and noninvasive tests for diagnosing H. pylori infection are the two categories of diagnostic techniques **[107]**.

Noninvasive methods include:

Urea Breath Tests (UBT): Two tests are available and have received FDA approval: ^{13}C & ^{14}C tests. Both offer reasonably priced, immediate results. A positive UBT indicates ongoing infection, that need treatment or another test with invasive procedures **[108]**. It is accurate in patients who underwent gastrectomy or recently have administered antibiotics or proton pump inhibitors (PPI), and it is excellent for assessing treatment response in children over the age of six**[109]**. False-negative results in recent treatments with bismuth, PPI and antibiotics, should not be used in children as a primary diagnosis due to high false-positive results in children under the age of six **[110]**, due to different CO2 production rate and also due to technical difficulties in performing 13C-UBT in young children as they are often unwilling to swallow the substrate, so oral urease–producing organisms can then split the substrate **[100]**.

Stool Antigen Test (SAT): This test uses antibodies to identify the presence of antigens for H. pylori in faeces based on enzyme immunoassay (EIA) or immunochromatography (ICA), allowing the confirmation of active infection either before treatment or after to assess the effectiveness of treatment **[111-113]**. It is inexpensive, not dependent on age, quick and simple, and helpful after therapy. False-negative outcomes in recent bismuth, PPI, and antibiotic treatments.

Serology: It depends on how an enzyme-linked immunosorbent assay (ELISA) measures the presence of immunoglobulin G (IgG) antibodies for H. pylori. IgG antibodies start to appear about three weeks after the infection starts, remain high for the duration of the infection, and then return to normal in about a year **[112]**. It is widely accessible and reasonably priced, and the results are unaffected by using PPI or other medications. Since the antibodies can still be detectable years after infection **[114]**, it is unable to differentiate between recent and past infections, sensitivity in children is also low, so it is not used to verify eradication.

Invasive methods:

The invasive techniques rely on biopsies obtained during gastroduodenal endoscopy; at least six biopsies from the antrum, greater and lesser curvatures, and the middle of the gastric body should be obtained to evaluate H. pylori gastritis. Additional biopsies may be needed if suspicious lesions such as ulcers or masses are found **[115]**.

Biopsies are used for rapid urea test, histological examination, the gold standard for diagnosis and H. pylori cultures **[79]**.

Histology is the first method used to detect H. pylori and is regarded as the benchmark in the confirmation of H. pylori infection. Although HE stain is almost enough for diagnosing H. pylori infection practically, immunohistochemical stain is the most sensitive and specific stain **[116, 117]**. It is useful to find the level of ongoing inflammation and activity, diagnose precancerous lesions like gastric intestinal metaplasia and grade of atrophy, and find malignancy and coccoid forms. PPI, antibiotics,

and the experience of pathologists are just a few of the variables that affect the accuracy of histology **[118]**.

Rapid urease test (RUT): it is cheap, quick, and precise **[119, 120]**. Furthermore, the gastric biopsy used for the RUT can be utilized for different tests, such as the H pylori PCR. Also, RUT is more sensitive than histology if there had been prior exposure to PPI and/or antibiotics **[121]**. False-negative results if there is GI hemorrhage and achlorhydria, or if the bacterial load in the biopsy is less than 10^4. Additionally, other urease-positive bacteria may produce false-positive results **[122]**.

Culture: It indicates an active infection and is advised whenever a treatment fails to find H. pylori that is fluoroquinolone- and clarithromycin-resistant **[123, 124]**. It has 100% specificity, and it provides antimicrobial resistance pattern. The quality of biopsy samples, the timing of the transport, and exposure to an aerobic environment are all factors in H. pylori cultivation **[124-127]**. Antibiotics should be avoided for at least four weeks prior to the culture because factors like low bacterial load, use of PPIs, antibiotics, alcohol, and bleeding can affect the outcome of the culture **[128, 129]**.

PCR: There are several commercial PCRs available to detect resistance to different antibiotics **[122]**. Compared to other methods, it is almost the most accurate method for H. pylori detection and antibiotic susceptibility testing in gastric biopsies **[130]**. False-positive results brought on by the finding of bacteria's dead DNA.

To sum up, availability and cost play a significant role in the test selection process. According to the most recent ESPGHAN/NASPGHAN guidelines, a diagnosis should include at least six gastric biopsies, histopathology, or culture and one other positive biopsy-based test. The guidelines also suggested that follow-up testing be done after 4 weeks of treatment with either the UBT or the SAT.

Monoclonal SAT is more appropriate in children under the age of 6 years (sensitivity: 88.0%-88.1%, specificity: 93%-94.2% %) because UBT was found to have a high rate of false positive results in this age group **[104]**.

MANEGEMENT IN CHILDERN

It is advised that the initial diagnosis of H. pylori infection be based on either a positive histopathology, a positive rapid urease test, or a positive culture, per Evidence-based Guidelines from ESPGHAN and NASPGHAN for H. pylori infection in Children **[104]**.

Indications for treatment

Eradication of the organism is advised in cases of H pylori-positive PUD. H. pylori treatment may be considered when infection is found using invasive methods in the absence of PUD.

Treatment can be considered to children who have H pylori infection and a first-degree relative with gastric cancer. The goal of therapy is to lower the opportunity of gastric cancer that may override the hazards of therapy in regions with a high prevalence of gastric cancer, like China or Japan **[131]**.

The ESPGHAN/NASPGHAN guidelines included a weak advisement for diagnosing and treating H pylori infection in patients with chronic ITP. However, more carefully planned interventional studies are needed to back up this suggestion **[132]**. Additionally, H pylori eradication therapy should be used in conjunction with iron supplementation if it is found that the infection is present in the context of refractory IDA.

Treatment regimens

Standard triple therapy, since 1996, first-line therapy, which includes two antimicrobials and PPI has been advised **[133]**. Recent data, however, indicate that this combination has become less effective and the rates of recovery have decreased to 80% in the majority of Asia-Pacific region as a result of clarithromycin (CLA) resistance **[134]**. As a result, alternatives have been created, including quadruple therapies that do not contain bismuth and those that do.

Sequential therapy (ST) involves PPI and amoxicillin (AMO) for five days, then PPI, metronidazole (MET) and CLA for another five days. In many nations, sequential therapy has shown more efficacy than seven or ten day standard triple therapy, with an eradication rate of between 73% and 81.4 percent **[135, 136]**.

Bismuth quadruple therapy (BQT) bismuth-based ten days quadruple treatment with bismuth sub-citrate, PPI, MET and AMO to eradicate *H. pylori* in pediatric patients is effective and secure. Use of this regimen is of special concern in patients those received treatment before and in case of dual antibiotics resistance **[137]**.

Concomitant therapy (CT) consisting of PPI, AMO, CLA, and MET was among the most efficient therapies with a high elimination rate, and it was demonstrated to be more efficient than triple therapy. Many reports suggest that in areas

that have strong antibiotic resistance or where testing for sensitivity is unavailable, BQT and CT can both be used as first-line treatments **[79]**. The treatment recommendations for children and adolescents have been updated by the ESPGHAN and NASPGHAN to increase the elimination rate after H. pylori infection. If the strain is sensitive to MET and CLA, then the triple therapy consisting of PPI (1-2 mg/kg/day), AMO (50 mg/kg/day), and CLA (20 mg/kg/day) for 2 weeks is the preferred course of action **[129]**.

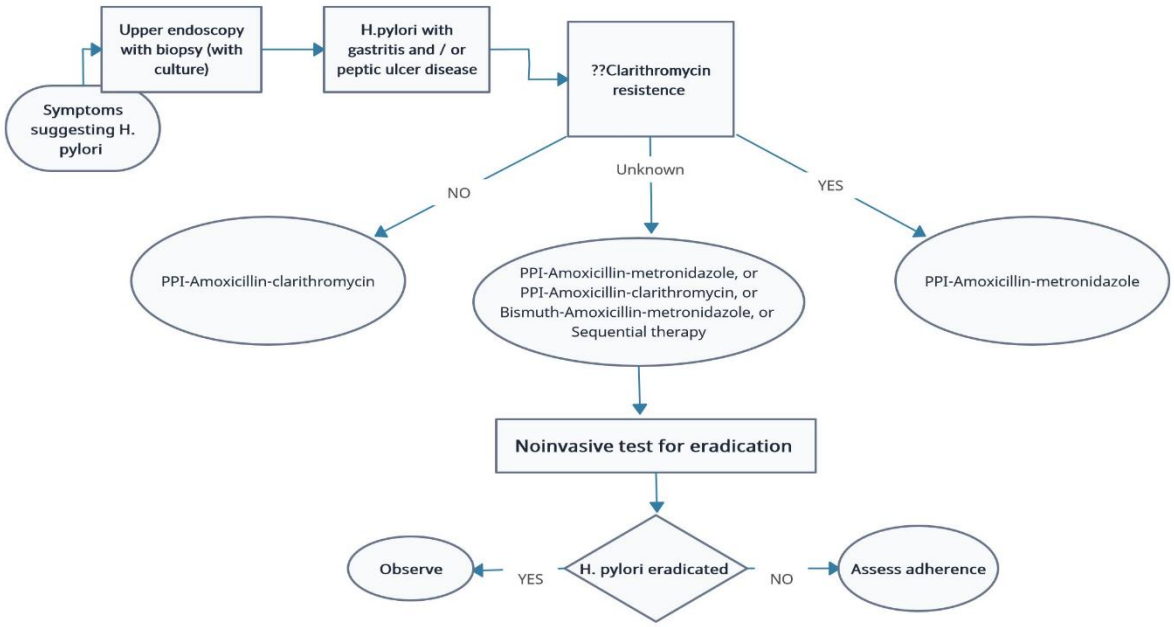

Fig. 1: Algorithm of H. pylori infection treatment in children **[58].**

Salvage therapy

If the triple therapy is unsuccessful, MET (20 mg/kg/day) can take the place of CLA without the need for additional antibiotic susceptibility testing. For pediatric patients infected with fully susceptible strains, ST lasting ten days (PPI and AMO for five days, then PPI, MET and CLA for five days) is an additional treatment option. In case of the strain is not sensitive to MET or CLA, ST should not be used.; however, this plan of treatment put the child in exposure to three antibiotics. BQT, which consists of bismuth salts (8 mg/kg/day), PPI, AMO (before the age of eight) or tetracycline (after the age of eight), and MET, is efficient in cases of resistance to both CLA and MET as well as when antibiotic sensitivity is unknown. The other regimen suggested in this situation combines high dose AMO triple therapy with MET, despite the limited available evidence **[104, 132]**. Antibiotic resistance is a significant issue that varies from region to region. The emergence of H. pylori CLA resistance is a result of the use of the macrolide class of antibiotics to treat respiratory tract infections **[138]**.

Causes of treatment failure

Antimicrobial resistance is rising globally and is the primary cause of H. pylori eradication failure **[139]**. A meta-analysis study was done to evaluate the resistance distribution of H. pylori to the most widely prescribed antibiotics, it was found that in Eastern Mediterranean region the highest antibiotic resistance was for metronidazole **[140]**. A study was done in one Egyptian university hospital to detect H. pylori antibiotic susceptibility to CLA, MET, fluroquinolones and AMO. The highest resistance found to be against clarithromycin , then amoxicillin **[141]**.

Antibiotic resistance is known to positively correlate with prior antibiotic use. The primary risk factor for the emergence of resistance to CLA in Europe appeared to be its use for other indications, primarily for respiratory tract infections **[139]**. There is higher rates of primary resistance of MET recorded in pediatric patients

from Africa and Asia that may be caused by the repeated use of metronidazole for parasitic or diarrheal diseases **[58]**. The most accurate method for predicting a patient's response to treatment is culture-based antibiotic susceptibility testing. However, the expense, time commitment, and reliance on biopsy from stomach mucosa make this an unsuitable option for determining first or second choice of treatment **[107]**.

Recurrence of infection after treatment makes H. pylori infection a chronic infection. Persister cells, which develop extremely strong persistence to a specific antibiotic without any genetic justification, are one of the main causes of chronic infections. Persister cells are still present after antibiotic therapy and the removal of nonpersister cells, which leads to an infection relapse. This procedure is repeatable numerous times and results in an untreatable infection **[142, 143]**.

Additionally, a reservoir for gastric infection and transmission may exist in the oral cavity **[144]**.

According to a study, when gastric infection with H. pylori was eradicated, the risk of H. pylori recurrence was less in the group receiving therapy for gastric and periodontal H. pylori than in the group that received only gastric treatment **[145]**.

Role of probiotics in management of H. pylori

Probiotic supplementation therapy is a newly developed method of treating H. pylori **[146]**. Probiotics are defined as live microorganisms that, when given to a host in sufficient quantities, have positive effects on their health **[147]**. The majority of probiotics are thought to inhabit the human GIT, and some species, like Lactobacillus spp., have been shown to colonize the stomach and either directly or indirectly compete with H. pylori **[148-150]**. Probiotics have been shown to reduce bacterial load when taken alone, but when combined with antibiotics, they have been shown to increase eradication rates and reduce side effects **[151, 152]**. However, the best dosage, timing, length of therapy, and mechanisms governing interactions between the chosen probiotics and antibiotics are still unknown **[146]**.

Vaccination against H. pylori

Epitope-based vaccines have become more popular recently as a result of changing trends in vaccine design**[153]**. Bacterial colonization and virulence factors have an effect on the pathogenesis of an H. pylori infection. The main prerequisite for its pathogenesis is colonization of the gastric mucosa, and adhesion comes before colonization. The flagellin A (FlaA) and FlaB dimer, of which FlaA is the principle flagellin and has a high immunogenicity, combine to form flagella, which have an important role in the adherence to GIT mucosa **[154]**. It could be used clinically to develop new vaccines **[155]**. Additionally, urease, a crucial component of H. pylori's virulence, is found on the bacteria's surface **[156]**. The two subunits that make up urease are urease A subunit (UreA) and urease B subunit (UreB), with the latter being the most promising candidate vaccine antigen due to its high immunogenicity and low toxicity **[157, 158]**.

Exotoxin VacA, which is secreted by H. pylori and causes host cells to develop vacuoles, has been suggested as a potential vaccine target**[159]**. The oncogenic factor **[160]** CagA, which is present in 50 to 70% of H. pylori species and is transported into gastric epithelium by bacterial production, is a target for vaccine development **[161]**.

To date, a lot of work has been incorporated into developing a vaccine for H. pylori, primarily in animal models. In these researches, cholera toxin, Escherichia coli (E. Coli) heat-labile enterotoxin (LT), synthetic oligodeoxynucleotides and aluminum hydroxides are the most frequently used adjuvants to increase vaccine efficacy **[162]**.

A randomized, double-blind, placebo-controlled phase 3 clinical trial on intact kids aged 6 to 15 discovered a significant decrease in infection in the kids who administered the vaccination after one year, with the beneficial results lasting for about three years. This discovery represents the biggest progress in developing an efficient H. pylori vaccine in humans till now **[163]**. The recombinant oral vaccine is made up of the H. pylori UreB subunit joined with the E. coli LT B subunit and is intended to stop a future natural infection rather than be used as a curative vaccine. Overall, the vaccine was immune-stimulating, secure, and safe, but extended follow-up studies are required before the WHO or FDA can approve its use **[163]**.

CONCLUSIONS

H. pylori is a chronic infection that is mostly acquired during childhood. The prevalence is widespread worldwide, it is more prevalent in developing nations owing to low socioeconomic conditions.

The two major toxins for pathogenesis are encrypted by the pathogenicity island (PAI); cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA).

The strains that infect either children or adults differ only slightly from one another, but the host response can differ from adults to children.

H. pylori is commonly believed to be asymptomatic in children, it also has been linked to the pathogenesis of gastrointestinal manifestations, abdominal pain is a frequent complaint mostly due to peptic ulcer disease.

Even though most of H. pylori infected patients may stay asymptomatic through their whole lives, nearly everyone develops chronic inflammation.

GI involvement range from mild antral gastritis, atrophic gastritis, peptic ulceration, and stomach cancer. H. pylori also is found to be linked to iron deficiency anemia and thrombocytopenia.

ESPGHAN and NASPGHAN guidelines declare that pediatric patients should not be treated using a "test and treat" strategy, which involves using a noninvasive test instead of an upper GIT endoscopy to establish H. pylori infection.

Diagnosis should include gastric biopsies, histopathology, or culture and one other positive biopsy-based test. The guidelines also suggested that follow-up testing be done after 1 month of therapy using the urea breath test or the stool antigen test.

Eradication of the organism is advised in cases of H pylori-related peptic ulcer disease. Treatment for H. pylori could be taken into consideration if H pylori infection is found using invasive tests in the absence of PUD. Also, treatment could be made available to children who have H pylori infection with a first-degree relative that has stomach cancer. Treatment regimens include standard triple therapy, sequential therapy, bisthmus quadrable therapy and concomitant therapy. Failure of treatment can be caused by drug resistance or incompliance. There are trials for vaccination for H. pylori, but longer follow-up studies are required before the WHO or FDA can approve its use.

REFERENCES

1. Fagoonee, S and R Pellicano. Helicobacter pylori: molecular basis for colonization and survival in gastric environment and resistance to antibiotics. A short review. *Infectious Diseases*, 2019. 51(6): p. 399-408.
2. Smith, S M. Role of Toll-like receptors in Helicobacter pylori infection and immunity. *World J Gastrointest Pathophysiol*, 2014. 5(3): p. 133.
3. Marshall, B and J R Warren. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *The lancet*, 1984. 323(8390): p. 1311-1315.
4. Iwańczak, B M, A M Buchner, and F Iwańczak. Clinical differences of Helicobacter pylori infection in children. *Adv Clin Exp Med*, 2017. 26(7): p. 1131-6.
5. Seo, J H, K Bortolin, and N L Jones. Helicobacter pylori infection in children. *Helicobacter*, 2020. 25: p. e12742.
6. Okuda, M, Y Lin, and S J H p i H D Kikuchi, Helicobacter pylori infection in children and adolescents. Helicobacter pylori in Human Diseases: Advances in Microbiology, Infectious Diseases and Public Health Volume 11. 2019:107-20.
7. Stefano, K, M Marco, G Federica, B Laura, B Barbara, and L Gioacchino. Helicobacter pylori, transmission routes and recurrence of infection: state of the art. *Acta Bio Medica*: Atenei Parmensis, 2018. 89(Suppl 8): p. 72.
8. Konno, M, S-i Yokota, T Suga, M Takahashi, K Sato, and N Fujii. Predominance of mother-to-child transmission of Helicobacter pylori infection detected by random amplified polymorphic DNA fingerprinting analysis in Japanese families. *The Pediatric infectious disease journal*, 2008. 27(11): p. 999-1003.
9. Pérez-Pérez, G I, R B Sack, R Reid, M Santosham, J Croll, and M J Blaser. Transient and persistent Helicobacter pylori colonization in Native American children. *J Clin Microbiol*, 2003. 41(6): p. 2401-2407.
10. Malaty, H M, A El-Kasabany, D Y Graham, C C Miller, S G Reddy, S R Srinivasan, et al. Age at acquisition of Helicobacter pylori infection: a follow-up study from infancy to adulthood. *The Lancet*, 2002. 359(9310): p. 931-935.
11. Goodman, K J and M Cockburn. The role of epidemiology in understanding the health effects of Helicobacter pylori. *Epidemiology*, 2001: p. 266-271.

12. Glynn, M K, C R Friedman, B D Gold, B Khanna, L Hutwagner, N Iihoshi, et al. Seroincidence of Helicobacter pylori infection in a cohort of rural Bolivian children: acquisition and analysis of possible risk factors. *Clin Infect Dis*, 2002. 35(9): p. 1059-1065.

13. Goodman, K J, K O'rourke, R S Day, C Wang, Z Nurgalieva, C V Phillips, et al. Dynamics of Helicobacter pylori infection in a US–Mexico cohort during the first two years of life. *Int J Epidemiol*, 2005. 34(6): p. 1348-1355.

14. Phillips, C V and K J Goodman. Interpreting data in the face of competing explanations: assessing the hypothesis that observed spontaneous clearance of Helicobacter pylori was all measurement error. *Int J Epidemiol*, 2009. 38(4): p. 1110-1117.

15. Eusebi, L, R Zagari, and F Bazzoli. Epidemiology of helicobacter pylori infection. *Helicobacter*, 19 (Suppl 1): 1–5. 2014.

16. Deeb, M M, W A Bahbah, D H Abou-Elela, and M M Hessen, Seroprevalence of Helicobacter pylori infection among school children in Al Qulubia governorate. *Menoufia Medical Journal*, 2018. 31(3): p. 963.

17. Kalach, N, P Bontems, and J Raymond. Helicobacter pylori infection in children. *Helicobacter*, 2017. 22: p. e12414.

18. Waskito, L A and Y Yamaoka, The story of Helicobacter pylori: depicting human migrations from the phylogeography. *Helicobacter pylori in Human Diseases: Advances in Microbiology, Infectious Diseases and Public Health Volume 11*. 2019:1-6.2019: p. 1-16.

19. Hanafiah, A and B S Lopes. Genetic diversity and virulence characteristics of Helicobacter pylori isolates in different human ethnic groups. *Infect Genet Evol*, 2020. 78: p. 104135.

20. Salama, N R, M L Hartung, and A Müller. Life in the human stomach: persistence strategies of the bacterial pathogen Helicobacter pylori. *Nat Rev Microbiol*, 2013. 11(6): p. 385-399.

21. Salama, N R. Cell morphology as a virulence determinant: lessons from Helicobacter pylori. *Curr Opin Microbiol*, 2020. 54: p. 11-17.

22. Kusters, J, M Gerrits, J Van Strijp, and C Vandenbroucke-Grauls. Coccoid forms of Helicobacter pylori are the morphologic manifestation of cell death. *Infect Immun*, 1997. 65(9): p. 3672-3679.

23. Reshetnyak, V I and T M Reshetnyak. Significance of dormant forms of Helicobacter pylori in ulcerogenesis. *World J Gastroenterol*, 2017. 23(27): p. 4867.

24. Reshetnyak, V I, A I Burmistrov, and I V Maev. Helicobacter pylori: Commensal, symbiont or pathogen? *World J Gastroenterol*, 2021. 27(7): p. 545.

25. Kao, C-Y, B-S Sheu, and J-J Wu. Helicobacter pylori infection: An overview of bacterial virulence factors and pathogenesis. *Biomed J*, 2016. 39(1): p. 14-23.

26. Saxena, A, A K Mukhopadhyay, and S P Nandi. Helicobacter pylori: Perturbation and restoration of gut microbiome. *J Biosci*, 2020. 45(1): p. 1-15.

27. Huang, Y, Q-l Wang, D-d Cheng, W-t Xu, and N-h Lu. Adhesion and invasion of gastric mucosa epithelial cells by Helicobacter pylori. *Front Cell Infect Microbiol*, 2016. 6: p. 159.

28. Alexander, S M, R J Retnakumar, D Chouhan, T N B Devi, S Dharmaseelan, K Devadas, et al. Helicobacter pylori in human stomach: the inconsistencies in clinical outcomes and the probable causes. *Front Microbiol*, 2021: p. 2277.

29. Hooi, J K, W Y Lai, W K Ng, M M Suen, F E Underwood, D Tanyingoh, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology*, 2017. 153(2): p. 420-429.

30. Crowe, S E. Helicobacter pylori infection. *N Engl J Med*, 2019. 380(12): p. 1158-1165.

31. Machlowska, J, P Kapusta, J Baj, F H Morsink, P Wołkow, R Maciejewski, et al. High-throughput sequencing of gastric cancer patients: unravelling genetic predispositions towards an early-onset subtype. *Cancers*, 2020. 12(7): p. 1981.

32.Goni, E and F Franceschi. Helicobacter pylori and extragastric diseases. *Helicobacter*, 2016. 21: p. 45-48.

33.McColl, K E. Helicobacter pylori infection. *N Engl J Med*, 2010. 362(17): p. 1597-1604.

34.Gravina, A G, R M Zagari, C De Musis, L Romano, C Loguercio, and M Romano. Helicobacter pylori and extragastric diseases: A review. *World J Gastroenterol*, 2018. 24(29): p. 3204.

35.Baj, J, A Forma, M Sitarz, P Portincasa, G Garruti, D Krasowska, et al. Helicobacter pylori virulence factors—mechanisms of bacterial pathogenicity in the gastric microenvironment. *Cells*, 2020. 10(1): p. 27.

36.Baj, J, I Korona-Głowniak, A Forma, A Maani, E Sitarz, M Rahnama-Hezavah, et al. Mechanisms of the epithelial–mesenchymal transition and tumor microenvironment in Helicobacter pylori-induced gastric cancer. *Cells*, 2020. 9(4): p. 1055.

37.Sharma, S A, M Tummuru, G G Miller, and M J Blaser. Interleukin-8 response of gastric epithelial cell lines to Helicobacter pylori stimulation in vitro. *Infect Immun*, 1995. 63(5): p. 1681-1687.

38.Handa, O, Y Naito, and T Yoshikawa. Helicobacter pylori: a ROS-inducing bacterial species in the stomach. *Inflamm Res*, 2010. 59(12): p. 997-1003.

39.Tiwari, S K, G Manoj, V Sharma, G Sivaram, R Saikant, A Bardia, et al. Relevance of Helicobacter pylori genotypes in gastric pathology and its association with plasma malondialdehyde and nitric oxide levels. *Inflammopharmacology*, 2010. 18(2): p. 59-64.

40.Slomiany, B and A Slomiany. Induction in gastric mucosal prostaglandin and nitric oxide by Helicobacter pylori is dependent on MAPK/ERK-mediated activation of IKK-β and cPLA2: modulatory effect of ghrelin. *Inflammopharmacology*, 2013. 21(3): p. 241-251.

41.Brawner, K, R Kumar, C Serrano, T Ptacek, E Lefkowitz, C Morrow, et al. Helicobacter pylori infection is associated with an altered gastric microbiota in children. *Mucosal immunology*. 2017; 10(5): p. 1169-1177.

42.Llorca, L, G Pérez-Pérez, P Urruzuno, M J Martinez, T Iizumi, Z Gao, et al. Characterization of the gastric microbiota in a pediatric population according to Helicobacter pylori status. *Pediatr Infect Dis J*, 2017. 36(2): p. 173-178.

43.Mohammad, M A, L Hussein. A Coward, and S J J P h n Jackson, Prevalence of Helicobacter pylori infection among Egyptian children: impact of social background and effect on growth. 2008. 11(3): p. 230-236.

44.Llorca, L, G Pérez-Pérez, P Urruzuno, M J Martinez, T Iizumi, Z Gao, et al. Characterization of the gastric microbiota in a pediatric population according to Helicobacter pylori status. *Pediatr Infect Dis J*, 2017. 36(2): p. 173-178.

45.Schulz, C, N Koch, K Schütte, D H Pieper, and P Malfertheiner. H. pylori and its modulation of gastrointestinal microbiota. *J Dig Dis*, 2015. 16(3): p. 109-117.

46.Alarcón, T, L Llorca, and G Perez-Perez. Impact of the microbiota and gastric disease development by Helicobacter pylori. *Molecular Pathogenesis and Signal Transduction by Helicobacter pylori*, 2017: p. 253-275.

47.Maldonado-Contreras, A, K C Goldfarb, F Godoy-Vitorino, U Karaoz, M Contreras, M J Blaser, et al. Structure of the human gastric bacterial community in relation to Helicobacter pylori status. *The ISME journal*, 2011. 5(4): p. 574-579.

48.Nejati, S, A Karkhah, H Darvish, M Validi, S Ebrahimpour, and H R Nouri. Influence of Helicobacter pylori virulence factors CagA and VacA on pathogenesis of gastrointestinal disorders. *Microb Pathog*, 2018. 117: p. 43-48.

49.Algood, H M S and T L Cover. Helicobacter pylori persistence: an overview of interactions between H. pylori and host immune defenses. *Clin Microbiol Rev*, 2006. 19(4): p. 597-613.

50.Harris, P R, S W Wright, C Serrano, F Riera, I Duarte, J Torres, et al. Helicobacter pylori gastritis in children is associated with a regulatory T-cell response. *Gastroenterology*, 2008. 134(2): p. 491-499.

51.de Melo, F F, G A Rocha, A M C Rocha, K N Teixeira, S H S P Pedroso, J B P Junior, et al. Th1 immune response to H. pylori infection varies according to the age of the patients and influences the gastric inflammatory patterns. *Int J Med Microbiol*, 2014. 304(3-4): p. 300-306.

52.Gil, J H, J W Seo, M-S Cho, J-H Ahn, and H Y Sung. Role of Treg and TH17 cells of the gastric mucosa in children with Helicobacter pylori gastritis. *J Pediatr Gastroenterol Nutr*, 2014. 58(2): p. 245-251.

53.Dore, M P, G Fanciulli, P A Tomasi, G Realdi, G Delitala, D Y Graham, et al. Gastrointestinal symptoms and Helicobacter pylori infection in school- age children residing in Porto Torres, Sardinia, Italy. *Helicobacter*, 2012. 17(5): p. 369-373.

54.Chen, X, W Liu, Y Shi, D Zhang, S Xiao, and G Tytgat. Helicobacter pylori associated gastric diseases and lymphoid tissue hyperplasia in gastric antral mucosa. *J Clin Pathol*, 2002. 55(2): p. 133-137.

55.Shiotani, A and D Y Graham. Pathogenesis and therapy of gastric and duodenal ulcer disease. *Medical Clinics*, 2002. 86(6): p. 1447-1466.

56.Weis, V G, J F Sousa, B J LaFleur, K T Nam, J A Weis, P E Finke, et al. Heterogeneity in mouse spasmolytic polypeptide-expressing metaplasia lineages identifies markers of metaplastic progression. *Gut*, 2013. 62(9): p. 1270-1279.

57.Arroyo, M T, M Forne, C M De Argila, F Feu, J Arenas, J De La Vega, et al. The prevalence of peptic ulcer not related to Helicobacter pylori or non- steroidal anti- inflammatory drug use is negligible in southern Europe. *Helicobacter*, 2004. 9(3): p. 249-254.

58.Koletzko, S, F Richy, P Bontems, J Crone, N Kalach, M L Monteiro, et al. Prospective multicentre study on antibiotic resistance of Helicobacter pylori strains obtained from children living in Europe. *Gut*, 2006. 55(12): p. 1711-1716.

59.Devanarayana, N M, C Adhikari, W Pannala, and S Rajindrajith. Prevalence of functional gastrointestinal diseases in a cohort of Sri Lankan adolescents: comparison between Rome II and Rome III criteria. *J Trop Pediatr*, 2011. 57(1): p. 34-39.

60.Zablah, R, C Velasco-Benítez, I Merlos, S Bonilla, and M Saps. Prevalence of functional gastrointestinal disorders in school-aged children in El Salvador. *Revista de Gastroenterología de México (English Edition)*, 2015. 80(3): p. 186-191.

61.Stanghellini, V, F K Chan, W L Hasler, J R Malagelada, H Suzuki, J Tack, et al. Gastroduodenal disorders. *Gastroenterology*, 2016. 150(6): p. 1380-1392.

62.Zhao, B, J Zhao, W-F Cheng, W-J Shi, W Liu, X-L Pan, et al. Efficacy of Helicobacter pylori eradication therapy on functional dyspepsia: a meta-analysis of randomized controlled studies with 12-month follow-up. *J Clin Gastroenterol*, 2014. 48(3): p. 241-247.

63.Moayyedi, P, S Soo, J Deeks, B Delaney, A Harris, M Innes, et al. Eradication of Helicobacter pylori for non- ulcer dyspepsia. *Cochrane Database of Systematic Reviews*, 2005(2).

64.Jin, X and Y m Li. Systematic review and meta- analysis from Chinese literature: the association between Helicobacter pylori eradication and improvement of functional dyspepsia. *Helicobacter*, 2007. 12(5): p. 541-546.

65.Sugano, K, J Tack, E J Kuipers, D Y Graham, E M El-Omar, S Miura, et al. Kyoto global consensus report on Helicobacter pylori gastritis. *Gut*, 2015. 64(9): p. 1353-1367.

66.Lupu, V, A Ignat, G Ciubotariu, A Ciubară, M Moscalu, and M Burlea. Helicobacter pylori infection and gastroesophageal reflux in children. *Diseases of the Esophagus*, 2016. 29(8): p. 1007-1012.

67.Moon, A, A Solomon, D Beneck, and S Cunningham-Rundles. Positive association between Helicobacter pylori and gastroesophageal reflux disease in children. *J Pediatr Gastroenterol Nutr*, 2009. 49(3): p. 283.

68.Khasag, O, G Boldbaatar, T Tegshee, D Duger, A Dashdorj, T Uchida, et al. The prevalence of Helicobacter pylori infection and other risk factors among Mongolian dyspeptic patients who have a high incidence

and mortality rate of gastric cancer. *Gut Pathog*, 2018. 10(1): p. 1-9.

69. Shavalipour, A, H Malekpour, H Dabiri, H Kazemian, H Zojaji, and M Bahroudi. Prevalence of cytotoxin-associated genes of Helicobacter pylori among Iranian GERD patients. *Gastroenterol Hepatol Bed Bench*, 2017. 10(3): p. 178.

70. Siupsinskiene, N, I Katutiene, V Jonikiene, D Janciauskas, and S Vaitkus. Helicobacter pylori in the tonsillar tissue: a possible association with chronic tonsillitis and laryngopharyngeal reflux. *J Laryngol Otol*, 2017. 131(6): p. 549-556.

71. Harris, P R, C A Serrano, A Villagrán, M M Walker, M Thomson, I Duarte, et al. Helicobacter pylori-associated hypochlorhydria in children, and development of iron deficiency. *J Clin Pathol*, 2013. 66(4): p. 343-347.

72. Azab, S F and A M Esh. Serum hepcidin levels in Helicobacter pylori-infected children with iron-deficiency anemia: a case–control study. *Ann Hematol*, 2013. 92(11): p. 1477-1483.

73. Kroot, J J, H Tjalsma, R E Fleming, and D W Swinkels. Hepcidin in human iron disorders: diagnostic implications. *Clin Chem*, 2011. 57(12): p. 1650-1669.

74. Ozkasap, S, N Yarali, P Isik, A Bay, A Kara, and B Tunc. The role of prohepcidin in anemia due to Helicobacter pylori infection. Pediatric *Hematology and Oncology*, 2013. 30(5): p. 425-431.

75. Hershko, C and A Ronson, Iron deficiency. Helicobacter infection and gastritis. *Acta Haematol*, 2009. 122(2-3): p. 97-102.

76. Kang, J M, N Kim, B H Lee, H K Park, H J Jo, C M Shin, et al.. Risk factors for peptic ulcer bleeding in terms of Helicobacter pylori, NSAIDs, and antiplatelet agents. *Scand J Gastroenterol*, 2011. 46(11): p. 1295-1301.

77. De Leest, H T, K S Steen, E Bloemena, W F Lems, E J Kuipers, M A Van de Laar, et al. Helicobacter pylori eradication in patients on long-term treatment with NSAIDs reduces the severity of gastritis: a randomized controlled trial. *J Clin Gastroenterol*, 2009. 43(2): p. 140-146.

78. Hershko, C and C Camaschella. How I treat unexplained refractory iron deficiency anemia. Blood, *The Journal of the American Society of Hematology*, 2014. 123(3): p. 326-333.

79. Malfertheiner, P, F Megraud, C O'morain, J Gisbert, E Kuipers, A Axon, et al. Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report. *Gut*, 2017. 66(1): p. 6-30.

80. Neunert, C, W Lim, M Crowther, A Cohen, L Solberg Jr, and M A Crowther. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood, *The Journal of the American Society of Hematology*, 2011. 117(16): p. 4190-4207.

81. Malnick, S D H, E Melzer, M Attali, G Duek, and J Yahav. Helicobacter pylori: friend or foe? *World J Gastroenterol*, 2014. 20(27): p. 8979.

82. Gasbarrini, A, F Franceschi, R Tartaglione, R Landolfi, P Pola, and G Gasbarrini. Regression of autoimmune thrombocytopenia after eradication of Helicobacter pylori. *The Lancet*, 1998. 352(9131): p. 878.

83. Arnold, D M, A Bernotas, I Nazi, R Stasi, M Kuwana, Y Liu, et al. Platelet count response to H. pylori treatment in patients with immune thrombocytopenic purpura with and without H. pylori infection: a systematic review. *haematologica*, 2009. 94(6): p. 850.

84. Kikuchi, T, T Kobayashi, T Yamashita, K Ohashi, H Sakamaki, and H Akiyama. Eight-year follow-up of patients with immune thrombocytopenic purpura related to H. pylori infection. *Platelets*, 2011. 22(1): p. 59-62.

85. Takahashi, T, T Yujiri, K Shinohara, Y Inoue, Y Sato, Y Fujii, et al. Molecular mimicry by Helicobacter pylori CagA protein may be involved in the pathogenesis of H. pylori- associated chronic idiopathic thrombocytopenic purpura. *Br J Haematol*, 2004. 124(1): p. 91-96.

86. O'Connor, H, A Axon, and M Dixon. Campylobacter-like organisms unusual in type A (pernicious anaemia) gastritis. *The Lancet*, 1984. 324(8411): p. 1091.

87.Stabler, S P. Vitamin B12 Deficiency. *N Engl J Med*, 2013. 368(2): p. 149-160.

88.Sarari, A S, M A Farraj, W Hamoudi, and T A Essawi. Helicobacter pylori, a causative agent of vitamin B12 deficiency. *The Journal of Infection in Developing Countries*, 2008. 2(05): p. 346-349.

89.Tsay, F-W and P-I Hsu. H. pylori infection and extra-gastroduodenal diseases. *J Biomed Sci*, 2018. 25: p. 1-8.

90.Thomas, J, A Dale, J Bunn, M Harding, W Coward, T Cole, et al. Early Helicobacter pylori colonisation: the association with growth faltering in The Gambia. *Archives of disease in childhood*, 2004. 89(12): p. 1149-1154.

91.Fialho, A M, A B Braga, D M Queiroz, M N Rodrigues, I D Herbster, and L L Braga. The association between Helicobacter pylori infection and height in children from an urban community in north-east Brazil. *Ann Trop Paediatr*, 2007. 27(1): p. 55-61.

92.Goodman, K J, P Correa, R Mera, M C Yepez, C Cerón, C Campo, et al. Effect of Helicobacter pylori infection on growth velocity of school-age Andean children. *Epidemiology (Cambridge, Mass.)*, 2011. 22(1): p. 118.

93.Dehghani, S M, H Karamifar, T Raeesi, and M Haghighat. Growth parameters in children with dyspepsia symptoms and Helicobacter pylori infection. *Indian Pediatr*, 2013. 50(3): p. 324-326.

94.Cherian, S, D Forbes, F Sanfilippo, A Cook, and D Burgner, Helicobacter pylori, helminth infections and growth: a cross- sectional study in a high prevalence population. *Acta Paediatr*, 2009. 98(5): p. 860-864.

95.Soylu, Ö B and Y Ozturk. Helicobacter pylori infection: effect on malnutrition and growth failure in dyspeptic children. *Eur J Pediatr*, 2008. 167(5): p. 557-562.

96.Chimonas, M A R, H C Baggett, A J Parkinson, P T Muth, E Dunaway, and B D Gessner. Asymptomatic Helicobacter pylori infection and iron deficiency are not associated with decreased growth among Alaska Native children aged 7–11 years. *Helicobacter*, 2006. 11(3): p. 159-167.

97.Franceschi, F, T Annalisa, D Di Rienzo Teresa, G Ianiro, S Franco, G Viviana, et al. Role of Helicobacter pylori infection on nutrition and metabolism. *World J Gastroenterol*, 2014. 20(36): p. 12809.

98.Annibale, B, G Capurso, and G Delle Fave. Consequences of Helicobacter pylori infection on the absorption of micronutrients. *Dig Liver Dis*, 2002. 34: p. S72-S77.

99.Taye, B, F Enquselassie, A Tsegaye, A Amberbir, G Medhin, A Fogarty, et al. Effect of Helicobacter pylori infection on growth trajectories in young Ethiopian children: a longitudinal study. *Int J Infect Dis*, 2016. 50: p. 57-66.

100. Jones, N L, S Koletzko, K Goodman, P Bontems, S Cadranel, T Casswall, et al. Joint ESPGHAN/NASPGHAN guidelines for the management of Helicobacter pylori in children and adolescents (update 2016). *J Pediatr Gastroenterol Nutr*, 2017. 64(6): p. 991-1003.

101. Tsigalou, C, T G Konstantinidis, D Cassimos, A Karvelas, A Grapsa, A Tsalkidis, et al. Inverse association between Helicobacter pylori infection and childhood asthma in Greece: a case-control study. *Germs*, 2019. 9(4): p. 182.

102. Akiner, U, H M Yener, E D Gozen, S B Kuzu, and S Canakcioglu. Helicobacter pylori in allergic and non-allergic rhinitis does play a protective or causative role? Eur Arch Otorhinolaryngol, 2020. 277(1): p. 141-145.

103. Cancer, I A f R o. A Review of Human Carcinogens. F. Chemical Agents and Related Occupations: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2012.

104. Koletzko, S, N L Jones, K J Goodman, B Gold, M Rowland, S Cadranel, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. *J Pediatr Gastroenterol Nutr*, 2011. 53(2): p. 230-243.

105. Koletzko, S, N L Jones, K J Goodman, B Gold, M Rowland, S Cadranel, et al. Evidence-based Guidelines From ESPGHAN and NASPGHAN for Helicobacter pylori Infection in Children. *J Pediatr Gastroenterol Nutr*, 2011. 53(2): p. 230-243.

106. Sierra, M S, E V Hastings, and K J J G M Goodman. What do we know about benefits of H. pylori treatment in childhood? *Gut Microbes*, 2013. 4(6): p. 549-567.

107. Calvet, X. Dealing with uncertainty in the treatment of Helicobacter pylori. *Ther Adv Chronic Dis*, 2018. 9(4): p. 93-102.

108. Ferwana, M, I Abdulmajeed, A Alhajiahmed, W Madani, B Firwana, R Hasan, et al. Accuracy of urea breath test in Helicobacter pylori infection: meta-analysis. *World J Gastroenterol*, 2015. 21(4): p. 1305.

109. Zhou, Q, L Li, Y Ai, Z Pan, M Guo, and J Han. Diagnostic accuracy of the 14C-urea breath test in Helicobacter pylori infections: a meta-analysis. *Wiener klinische Wochenschrift*, 2017. 129(1): p. 38-45.

110. Zhu, R, K Chen, Y-Y Zheng, H-W Zhang, J-S Wang, Y-J Xia, et al. Meta-analysis of the efficacy of probiotics in Helicobacter pylori eradication therapy. *World J Gastroenterol*, 2014. 20(47): p. 18013.

111. Best, L M, Y Takwoingi, S Siddique, A Selladurai, A Gandhi, B Low, et al. Non- invasive diagnostic tests for Helicobacter pylori infection. *Cochrane Database of Systematic Reviews*, 2018(3).

112. Shimoyama, T. Stool antigen tests for the management of Helicobacter pylori infection. *World J Gastroenterol*, 2013. 19(45): p. 8188.

113. Kodama, M, K Murakami, T Okimoto, Y Fukuda, T Shimoyama, M Okuda, et al. Influence of proton pump inhibitor treatment on Helicobacter pylori stool antigen test. *World J Gastroenterol*, 2012. 18(1): p. 44.

114. Lopes, A I, F F Vale, and M Oleastro. Helicobacter pylori infection-recent developments in diagnosis. *World J Gastroenterol*, 2014. 20(28): p. 9299.

115. White, J R, S S Sami, D Reddiar, J Mannath, J Ortiz-Fernández-Sordo, S Beg, et al. Narrow band imaging and serology in the assessment of premalignant gastric pathology. *Scand J Gastroenterol*, 2018. 53(12): p. 1611-1618.

116. Hartman, D J and S R Owens. Are routine ancillary stains required to diagnose Helicobacter infection in gastric biopsy specimens? An institutional quality assurance review. *Am J Clin Pathol*, 2012. 137(2): p. 255-260.

117. Batts, K P, S Ketover, S Kakar, A M Krasinskas, K A Mitchell, R Wilcox, et al. Appropriate use of special stains for identifying Helicobacter pylori: recommendations from the Rodger C. Haggitt Gastrointestinal Pathology Society. *Am J Surg Pathol*, 2013. 37(11): p. e12-e22.

118. Malfertheiner, P, F Megraud, C A O'Morain, J Atherton, A T Axon, F Bazzoli, et al. Management of Helicobacter pylori infection—the Maastricht IV/Florence consensus report. *Gut*, 2012. 61(5): p. 646-664.

119. Tseng, C-A, W-M Wang, and D-C Wu. Comparison of the clinical feasibility of three rapid urease tests in the diagnosis of Helicobacter pylori infection. *Dig Dis Sci*, 2005. 50(3): p. 449-452.

120. Monteiro, L, A De Mascarel, A M Sarrasqueta, B Bergey, C Barberis, P Talby, et al. Diagnosis of Helicobacter pylori infection: noninvasive methods compared to invasive methods and evaluation of two new tests. *Am J Gastroenterol*, 2001. 96(2): p. 353-358.

121. Dechant, F-X, R Dechant, A Kandulski, M Selgrad, F Weber, U Reischl, et al. Accuracy of different rapid urease tests in comparison with histopathology in patients with endoscopic signs of gastritis. *Digestion*, 2020. 101(2): p. 184-190.

122. Pohl, D, P M Keller, V Bordier, and K Wagner. Review of current diagnostic methods and advances in Helicobacter pylori diagnostics in the era of next generation sequencing. *World J Gastroenterol*, 2019. 25(32): p. 4629.

123. Graham, D Y and M Miftahussurur. Helicobacter pylori urease for diagnosis of Helicobacter pylori infection: A mini review. *J Adv Res*, 2018. 13: p. 51-57.

124. Dolak, W, C Bilgilier, A Stadlmann, J Leiner, A Püspök, W Plieschnegger, et al. A multicenter prospective study on the diagnostic performance of a new liquid rapid urease test for the diagnosis of Helicobacter pylori infection. *Gut Pathog*, 2017. 9(1): p. 1-5.

125. Kuhns, L G, S L Benoit, K Bayyareddy, D Johnson, R Orlando, A L Evans, et al. Carbon fixation driven by molecular hydrogen results in chemolithoautotrophically enhanced growth of Helicobacter pylori. *J Bacteriol*, 2016. 198(9): p. 1423-1428.

126. Hortelano, I, Y Moreno, F J Vesga, and M A Ferrús. Evaluation of different culture media for detection and quantification of H. pylori in environmental and clinical samples. *International Microbiology*, 2020. 23(4): p. 481-487.

127. Peretz, A, M Paritsky, N Pastukh, A Koifman, D Brodsky, T Glyatman, et al. Improvement and optimization of the classical gastric biopsy culture technique for Helicobacter pylori diagnosis using trypsin. *J Med Microbiol*, 2015. 64(6): p. 642-645.

128. Leszczyńska, K, A Namiot, Z Namiot, J Leszczyńska, P Jakoniuk, M Chilewicz, et al. Patient factors affecting culture of Helicobacter pylori isolated from gastric mucosal specimens. *Adv Med Sci*, 2010. 55(2): p. 161-166.

129. Mégraud, F J G. H pylori antibiotic resistance: prevalence, importance, and advances in testing. *Gut*, 2004. 53(9): p. 1374-1384.

130. Szymczak, A, S Ferenc, J Majewska, P Miernikiewicz, J Gnus, W Witkiewicz, et al. Application of 16S rRNA gene sequencing in Helicobacter pylori detection. *PeerJ*, 2020. 8: p. e9099.

131. Leontiadis, G I and A C J B c e Ford. Helicobacter pylori eradication: gastric cancer prevention. *BMJ Clinical Evidence*. 2015; 2015.

132. Jones, N L, S Koletzko, K Goodman, P Bontems, S Cadranel, T Casswall, et al. Joint ESPGHAN/NASPGHAN guidelines for the management of Helicobacter pylori in children and adolescents (update 2016). *J Pediatr Gastroenterol Nutr*, 2017. 64(6): p. 991-1003.

133. Drumm, B, S Koletzko, and G Oderda. Medical position paper: The European Society for Pediatric Gastroenterology and Nutrition Helicobacter pylori infection in children: a consensus statement. *J Pediatr Gastroenterol Nutr*, 2000. 30: p. 207-213.

134. Kim, J S, B-W Kim, S J Hong, J I Kim, K-N Shim, J-H Kim, et al. Sequential therapy versus triple therapy for the first line treatment of Helicobacter pylori in Korea: a nationwide randomized trial. *Gut Liver*, 2016. 10(4): p. 556.

135. Huang, J, L Zhou, L Geng, M Yang, X W Xu, Z L Ding, et al. Randomised controlled trial: sequential vs. standard triple therapy for H elicobacter pylori infection in Chinese children–a multicentre, open- labelled study. *Aliment Pharmacol Ther*, 2013. 38(10): p. 1230-1235.

136. Huang, Y and X J T I J o P Zhan. Sequential therapy is superior to triple therapy for Helicobacter pylori infection in children: a meta-analysis. *Indian J Pediatr*, 2016. 83(4): p. 307-315.

137. Kotilea, K, S Cadranel, A Salame, J Nguyen, T Mahler, V Y Miendje Deyi, et al. Efficacy and safety of bismuth- based quadruple therapy for Helicobacter pylori eradication in children. *Helicobacter*, 2021. 26(4): p. e12825.

138. Mégraud, F. H pylori antibiotic resistance: prevalence, importance, and advances in testing. *Gut*, 2004. 53(9): p. 1374-1384.

139. Lim, S G, R W Park, S J Shin, D Yoon, J K Kang, J C Hwang, et al. The relationship between the failure to eradicate Helicobacter pylori and previous antibiotics use. *Dig Liver Dis*, 2016. 48(4): p. 385-390.

140. Savoldi, A, E Carrara, D Y Graham, M Conti, and E Tacconelli. Prevalence of antibiotic resistance in Helicobacter pylori: a systematic review and meta-analysis in World Health Organization regions. *Gastroenterology*, 2018. 155(5): p. 1372-1382. e17.

141. Zaki, M, W Othman, M A Ali, and A Shehta. Fluoroquinolone-resistant Helicobacter pylori strains isolated from one Egyptian University Hospital: molecular aspects. *J Microbiol Antimicrobial Agents*, 2016. 2: p. 26-31.

142. Zali, M R. Facing resistance of H. pylori infection. *Gastroenterol Hepatol Bed Bench*, 2011. 4(1): p. 3.

143. Fisher, R A, B Gollan, and S Helaine. Persistent bacterial infections and persister

cells. *Nat Rev Microbiol*, 2017. 15(8): p. 453-464.

144. Rasmussen, L T, R W d Labio, L L Gatti, L C d Silva, V F d Queiroz, M d A C Smith, et al. Helicobacter pylori detection in gastric biopsies, saliva and dental plaque of Brazilian dyspeptic patients. *Memorias do Instituto Oswaldo Cruz*, 2010. 105(3): p. 326-330.

145. Tongtawee, T, W Wattanawongdon, and T Simawaranon. Effects of periodontal therapy on eradication and recurrence of Helicobacter pylori infection after successful treatment. *J Int Med Res*, 2019. 47(2): p. 875-883.

146. Chey, W D, G I Leontiadis, C W Howden, and S F Moss. ACG clinical guideline: treatment of Helicobacter pylori infection. *Am J Gastroenterol*, 2017. 112(2): p. 212-239.

147. Dore, M P, S Bibbo, G M Pes, R Francavilla, and D Y Graham. Role of probiotics in Helicobacter pylori eradication: lessons from a study of Lactobacillus reuteri strains DSM 17938 and ATCC PTA 6475 (Gastrus®) and a proton-pump inhibitor. *Can J Infect Dis Med Microbiol*, 2019. 2019.

148. Francavilla, R, E Lionetti, S P Castellaneta, A M Magistà, G Maurogiovanni, N Bucci, et al. Inhibition of Helicobacter pylori infection in humans by Lactobacillus reuteri ATCC 55730 and effect on eradication therapy: a pilot study. *Helicobacter*, 2008. 13(2): p. 127-134.

149. Ryan, K A, T Jayaraman, P Daly, C Canchaya, S Curran, F Fang, et al. Isolation of lactobacilli with probiotic properties from the human stomach. *Lett Appl Microbiol*, 2008. 47(4): p. 269-274.

150. Espinoza, J L, A Matsumoto, H Tanaka, and I Matsumura. Gastric microbiota: An emerging player in Helicobacter pylori-induced gastric malignancies. *Cancer Lett*, 2018. 414: p. 147-152.

151. Homan, M and R Orel. Are probiotics useful in Helicobacter pylori eradication? *World J Gastroenterol*, 2015. 21(37): p. 10644.

152. Song, H, L Zhou, D Liu, L Ge, and Y Li. Probiotic effect on Helicobacter pylori attachment and inhibition of inflammation in human gastric epithelial cells. *Exp Ther Med*, 2019. 18(3): p. 1551-1562.

153. Ru, Z, M Yu, Y Zhu, Z Chen, F Zhang, Z Zhang, et al. Immmunoinformatics- based design of a multi- epitope vaccine with CTLA- 4 extracellular domain to combat Helicobacter pylori. *FASEB J*, 2022. 36(4): p. e22252.

154. Gu, H. Role of Flagella in the Pathogenesis of Helicobacter pylori. *Curr Microbiol*, 2017. 74(7): p. 863-869.

155. Yan, J, S-H Liang, Y-F Mao, L-W Li, and S-P Li. Construction of expression systems for flaA and flaB genes of Helicobacter pylori and determination of immunoreactivity and antigenicity of recombinant proteins. *World J Gastroenterol*, 2003. 9(10): p. 2240.

156. Wang, B, X Pan, H Wang, Y Zhou, J Zhu, J Yang, et al. Immunological response of recombinant H. pylori multi-epitope vaccine with different vaccination strategies. *Int J Clin Exp Pathol*, 2014. 7(10): p. 6559.

157. Blanchard, T G and S J Czinn. Identification of Helicobacter pylori and the evolution of an efficacious childhood vaccine to protect against gastritis and peptic ulcer disease. *Pediatr Res*, 2017. 81(1): p. 170-176.

158. Pan, X, H Ke, X Niu, S Li, J Lv, and L Pan. Protection against Helicobacter pylori infection in BALB/c mouse model by oral administration of multivalent epitope-based vaccine of cholera toxin B subunit-HUUC. *Front Immunol*, 2018. 9: p. 1003.

159. Liu, X-L, S-Q Li, C-J Liu, H-X Tao, and Z-S Zhang. Antigen epitope of Helicobacter pylori vacuolating cytotoxin A. *World J Gastroenterol*, 2004. 10(16): p. 2340.

160. Takahashi-Kanemitsu, A, C T Knight, and M Hatakeyama. Molecular anatomy and pathogenic actions of Helicobacter pylori CagA that underpin gastric carcinogenesis. *Cellular & molecular immunology*, 2020. 17(1): p. 50-63.

161. Stein, M, P Ruggiero, R Rappuoli, and F Bagnoli. Helicobacter pylori CagA: from pathogenic mechanisms to its use as an anti-cancer vaccine. *Front Immunol*, 2013: p. 328.

162. Mirzaei, N, F Poursina, S Moghim, N Rashidi, and H Ghasemian Safaei. The study of H. pylori putative candidate factors for single-and multi-component vaccine development. *Crit Rev Microbiol*, 2017. 43(5): p. 631-650.

163. Zeng, M, X-H Mao, J-X Li, W-D Tong, B Wang, Y-J Zhang, et al. Efficacy, safety, and immunogenicity of an oral recombinant Helicobacter pylori vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, 2015. 386(10002): p. 1457-1464.