European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:1035–1045
https://doi.org/10.1007/s10096-019-03502-5

REVIEW

Helicobacter pylori infection in children: an overview of diagnostic methods

Parisa Sabbagh[1] · Mostafa Javanian[1] · Veerendra Koppolu[2] · VeneelaKrishna Rekha Vasigala[3] · Soheil Ebrahimpour[1]

Received: 8 January 2019 / Accepted: 31 January 2019 / Published online: 7 February 2019

Abstract

Children differ from adults regarding *Helicobacter pylori* (*H. pylori*) infection in many terms. *H. pylori* infection represents a key factor in the pathogenesis of duodenal ulcer and chronic gastritis in children. *H. pylori* infection causes some extraintestinal diseases as well as gastrointestinal diseases. Although, among these illnesses in children, symptoms like recurrent abdominal pain are not specific. Moreover, the role of the pathogen in the growth faltering, iron deficiency anemia, and asthma still remains controversial. A reliable method to detect *H. pylori* infection is a crucial issue, sand is still a matter of active debate. The tests applied for *H. pylori* diagnosis are grouped as either invasive or non-invasive methods. Invasive methods consist of endoscopic evaluation, the rapid urease test (RUT), histology, and bacterial culture. Non-invasive tests include the urea breath test (UBT), stool antigen test (SAT), serology, and molecular diagnostic approaches. Use of endoscopy is a pre-requisite for all invasive methods and poses difficulties in children as it is a difficult procedure and requires patient's cooperation. For this reason, the non-invasive tests have been commonly used in children, although their accuracy is not very reliable in some cases. Invasive tests may be opted to confirm the diagnosis as and when needed. This review presents the diagnostic tests used to detect *H. pylori* infection in children.

Keywords *Helicobacter pylori* · Diagnosis · Children

Introduction

For the first time in 1983, Robin Warren observed a curved bacteria in the mucosal layer of the gastric biopsy specimen. Subsequently, with the help of Berry Marshall, the organism was isolated from the gastric biopsy specimens and named "Campylobacter pyloridis" [1], and was later renamed as *Helicobacter pylori* (*H. pylori*) [1–3].

Since the initial identification of the *H. pylori*, the bacterium was found to be associated to many diseases including chronic gastritis (usually asymptomatic, especially in children), peptic ulcer disease (PUD), gastric mucosa associated lymphoid tissue lymphoma (MALT), and gastric adenocarcinoma [4–9]. However, the association between this organism and gastroduodenal complaints in children is not fully clear [10].

H. pylori is the most common pathogen with prevalence rates of more than 80% in developing countries and less than 40% in developed countries [11]. *H. pylori* infection is predominantly acquired in childhood and continues throughout the life, unless specific treatment is prescribed [10, 12, 13]. *H. pylori* infection was first suspected in children with chronic active gastritis symptoms undergoing upper gastrointestinal endoscopy. Consequently, many further studies conducted at *H. pylori* in children identified *H. pylori* as the key pathogenic bacterium in pediatric gastroenterology [14].

Diagnostic methods for *H. pylori* infection are categorized as invasive and non-invasive tests. The invasive tests include an upper gastrointestinal endoscopy followed by testing of biopsy samples using methods such as rapid urease test (RUT), histology, and bacterial culture. The non-invasive tests include the urea breath test (UBT), stool antigen test (SAT), and serology. Polymerase chain reaction (PCR) can be classified as both invasive and non-invasive test depending on the

✉ Soheil Ebrahimpour
drsoheil1503@yahoo.com

[1] Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Islamic Republic of Iran

[2] Scientist Biopharmaceutical Development Medimmune Gaithersburg, Gaithersburg, MD 20878, USA

[3] Rangaraya Medical College, NTR University of Health Sciences, Kakinada, India

samples used for the testing (Table 1) [15]. Non-invasive tests have been the most commonly used *H. pylori* diagnosis methods in children, although their accuracy is not very reliable in some cases. This may be due to the fact that applying endoscopy test in children is not recommended. The underlying review is a collection of all the possible diagnostic approaches that can be implemented to detect *H. pylori* infection in children [16, 17].

Microbiology

H. pylori is a spiral, microaerophilic, gram-negative, slow-growing, and flagellated bacterium [4, 18]. The surface of *H. pylori* is coated with urease and thermal shock protein [19].

H. pylori produces large amounts of surface-localized urease which acts as an important colonization factor. Using this enzyme, the bacterium breaks urea to release ammonia, causing an increase in the pH of the gastric antrum for bacterial survive in the acid environment. This enzyme is important for bacterial colonization and is an indirect marker for the presence of bacteria [10]. Vacuolating cytotoxin (VacA) is a virulence factor of *H. pylori* that induces pro-inflammatory response and multiple cellular activities that facilitate chronic colonization of the gastric mucosa. This protein is able to induce vacuolation in eukaryotic cells [20]. All of the *H. pylori* strains have VacA gene, but only 50% of them expresses a mature VacA protein [20, 21]. VacA inserted into the membranes of endosomal vesicles to form pores [8, 20]. These changes the structure of the anions within the endosomes and consequently leads to osmotic swelling, which can have effects on the gastric epithelium. Furthermore, it also induces apoptosis, leading to cell death [22, 23].

Cytotoxin-associated antigen (CagA) is possibly the most important virulence factor in *H. pylori*. CagA-positive strains contribute to the inflammatory responses by *H. pylori* through activation of certain cytokines and NF-κB signaling. *H. pylori* also produces catalase that supports the survival of *H. pylori* in the host by preventing the formation of reactive oxygen metabolites from hydrogen peroxide. Also, the lipopolysaccharides (LPS) as an endotoxin enhances the ability of *H. pylori* to colonize in the stomach (Table 2) [24].

As soon as the *H. pylori* colonizes the stomach and releases virulence factors into the host cells, the host immune system is activated to build a strong immune response and inflammation of gastric mucosa. Innate immune receptors of host epithelial cells such as Tol-like receptors (TLR) activate NF-κB signaling to express pro-inflammatory cytokines. Immune system is further activated through recruitment of inflammatory cells at the infection site, and enhances the production of pro-inflammatory and anti-inflammatory cytokines. The activation of immune response further enhance the production of reactive oxygen species by increasing oxidative stress leading to cell damage, DNA damage, and favoring the carcinogenesis process [25].

Further description is that against these bacterial activities, the host immune system begins to build and secrete some cytokines and activates inflammation-enhancing cells. So that

Table 1 Advantages and limitations of various diagnostic methods regarding to *Helicobacter pylori* infection in children

Methods		Advantages	Limitations
Non-invasive	Urea breath test	High accuracy; useful before and after treatment	Low specificity and high false-positive results in young children (< 6 years old); false-negative results in patients recipient bismuth, antibiotics
	Stool antigen test	Fast, easy, and cost-effective; no age dependency; useful before and after therapy	False-negative results in patients recipient bismuth, antibiotics; dependency of accuracy on the cut-off value and treatment status
	Serology	Inexpensive; cheapest; widely available	Inability to detect acute versus chronic infection; sensitivity in children is low; not reliable to confirm the eradication of the infection
Invasive	Histology	Observation the grade of atrophy, inflammation rates, gastric intestinal metaplasia, and malignancy	Observer-dependency; time-consuming; need special skills, and costly; dependence of accuracy on the receiver of antibiotics, proton-pump inhibitors
	Rapid urease test	High sensitivity (80%) and specificity (almost 100%); rapid, inexpensive	Dependence of accuracy on the number and location of the biopsies, bacteria density, receive of antibiotics, proton-pump inhibitors, bismuth, achlorhydria, and the prevalence rate of infection
	Culture	Determination of pattern of antimicrobial resistance; high specificity (100%)	Expensive, and time-consuming test; dependency of sensitivity on the staff skill, and culture media
Non-invasive or invasive	Polymerase chain reaction	Fast; high sensitivity and specificity; determination of antimicrobial susceptibility	False-positive results due to detect DNA pieces of dead bacteria

Table 2 Introducing some virulence factors of *H. pylori*

Virulence factors	Function
Urease	Crucial role in the *H. pylori* colonization; serious damage to the epithelium via NH3 production; helping to produce inflammatory cytokines
Catalase	Protection of *H. pylori* against the damaging effects of hydrogen peroxide
Vacuolating cytotoxin A (*VacA*)	Vacuolization; apoptosis of gastric epithelial cells
Cytotoxin-associated antigen (*CagA*)	Oncoprotein; association with adjustment disorder of Wnt/β-catenin signaling
Outer inflammatory protein A (*OipA*)	Helping to translocation of the CagA into gastric cells; gastric inflammation via IL-8; association with *H. pylori* density
Duodenal ulcer promoting gene A(*dupA*)	One of the specific marker for duodenal ulcer and even gastric cancer; association to production of inflammatory cytokines
Sialic acid-binding adhesion (*SabA*)	Intervention and help to *H. pylori* binding to inflamed gastric mucosa and red blood cells
Blood-group-antigen-binding adhesion (*BabA*)	Involvement in the attachment of *H. pylori* to gastric mucosa
Gamma-glutamyltranspeptidase (GGT)	Engagement in inflammation of gastric mucosa via upregulation of IL-8 and activation of NF-kB

higher level of IL-1β, IL-8, and IL-18 and the number of macrophages in the gastric mucosa are found. The amount of TGF-β production of dendritic cells increases dramatically, which subsequently increases the activity of regulatory T cells (Treg). Treg cells lead to increased bacterial density and reducing inflammation, all of which contribute to the presence of *H. pylori* in the stomach, and ultimately contribute to chronic infection (Fig. 1) [26].

Epidemiology

About half of the world's population is known to be infected with *H. pylori* and is predominantly acquired in early childhood [4, 27] and person-to-person contact within the family appears to be the key transmission route (via the fecal-oral and oral- oral or gastro-oral route) [28, 29]. Sources of transmission of infection from the environment such as water and contaminated vegetables are also approved. Several studies have shown that children often receive *H. pylori* infection from their infected mothers or siblings. As such, studies show that these infected mothers are the critical source of *H. pylori* infection of their children [30, 31]. This transmission is mainly done through contact with the infected mother's mouth via kissing or testing the quality of food by the mother. Overall, the seroprevalence rate of *H. pylori* in children estimated within 30% [32]. In developing countries, such as Latin America, Asia, the Caribbean, and Africa, the prevalence rates are much higher (almost 60%) than developed regions, such as Western Europe and North America (less than 10%) [33–35]. All of these statistics show that several factors affect the prevalence of *H. pylori* infection in children, including low socioeconomic status, poor hygiene status, household crowding, family education, gender, age, and geographical area. This means that the risk factors in the acquisition of *H. pylori* infection in kids differs among various populations and areas [36–40]. Infection rates in developed countries have declined dramatically in recent decades, and also, the mentioned reduction in children has been much higher compared to adults [41]. According to the reports of the National Health and Nutrition Examination Survey (NHANES) in 1996, the prevalence of *H. pylori* infection in the age group of 6 to19 years was 24.8% [42]. In another study in Texas in 2012, the rate of infection in the age group less than 20 years decreased to 6.0% [43]. In Russia, among the children under the age of five, the seroprevalence of *H. pylori* declined from 30% in 1995 to 2% in 2005 [44]. Recently, some studies in Asian countries also show a decrease in infection rate compared to the past decades [45].

Clinical manifestations

The clinical manifestations of *H. pylori* infection are not very clearly defined in children. The infection is supposed to be acquired in early childhood, but complex host bacterium relationship determines the clinical manifestations of the disease. In about 85% of *H. pylori* infected individuals, the bacteria remains life long as asymptomatic [46]. However, *H. pylori* can cause peptic/gastric ulcers in about 10% individuals, and gastric cancer in 1% individuals [47]. *H. pylori* is one of the main causes of duodenal ulcer and chronic gastritis in children. *H. pylori* is also suspected to cause other illnesses such as recurrent abdominal pain (RAP) and iron deficiency anemia (IDA).

Gastrointestinal manifestations

Necessarily, in all children with *H. pylori* infection, there are no gastrointestinal manifestations, in other words, these symptoms are non-specific during *H. pylori* infection in children.

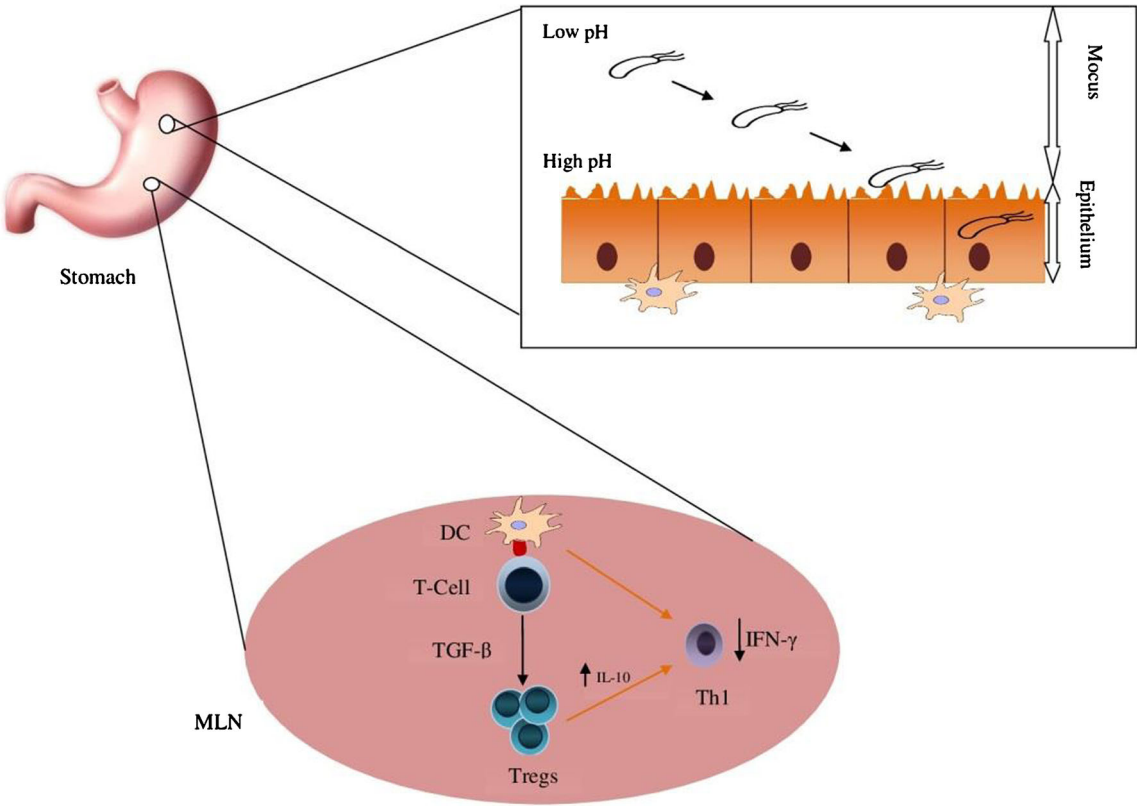

Fig. 1 Binding and entering of *H. pylori* to epithelial cells results in the production of higher number of dendritic cells in the gastric mucosa are found. The amount of TGF-β production in dendritic cells and T cells increases, which consequently increases the activity of regulatory T cells (Treg). The level of IL-10 production by the Treg cells increases, which along with the activity of the dendritic cells, reduces function of Thelper cell (Th) and IFN-γ production. Therefore, Treg cells lead to increased bacterial density and contribute to chronic infection

Recurrent abdominal pain

After about 40 years of isolating *H. pylori*, its association with RAP has been one of the most controversial challenges in pediatric gastroenterology. Many researchers around the world have reported an association between *H. pylori* and abdominal pain, while many surveys contradicted this view [48, 49]. Masoodpour et al. did not observe any association between RAP and *H. pylori* infection in children aged 5–15 years [50]. In meta-analysis between 1966 and 2009, Spee et al. found no association between RAP and *H. pylori* infection in children [51].

Gastroesophageal reflux disease (GERD)

The role of *H. pylori* in GERD is still controversial; thus both positive and negative associations between *H. pylori* and GERD were reported recently [52, 53]. Daugule et al. showed a significantly higher prevalence of *H. pylori* among patients with reflux esophagitis compared to cases with hyperaemic gastropathy [54]. The prevalence of reflux esophagitis was 14.2% among *H. pylori*-positive and 3.3% among *H. pylori*-negative patients. However, in some studies, an inverse correlation of *H. pylori* infection with the prevalence of gastro-esophageal reflux disease was noticed [55]. Accordingly, some studies have shown that eradication of *H. pylori* was the only predictor of gastro-esophageal treatment failure [56]. Eradication of *H. pylori* increases the esophageal acid exposure and might adversely affect the clinical course of reflux disease [57, 58]. Furthermore, some scientists from Turkey did not find a positive association between *H. pylori* infection and severity of esophagitis [53].

Gastritis and peptic ulcer diseases

*H. pylori*infection is the main factor in the development of gastritis and PUD [59, 60]. *H. pylori* infection have a two- to sixfold increased risk of developing gastric cancer and MALT [61].

In children, the number of these bacteria in the gastric mucosa is frequently lower than that of adults [62]. Studies have shown that the rate ratio of gastritis in children with *H. pylori* infection was 1.9 to 71% compared to non-infectious children. The prevalence of *H. pylori* infection in children with duodenal ulcer was high (range, 33 to 100%; median, 92%) compared with children with gastric ulcer (range, 11 to 75%; median,

25%) [63]. A retrospective study from Japan showed that the prevalence of *H. pylori* was very high in antral gastritis and duodenal ulcer patients (98.5% and 83%, respectively) [64].

Extraintestinal manifestations

In addition to the gastrointestinal diseases, *H. pylori* infection may also play a role in some extraintestinal diseases.

Iron deficiency anemia

Several studies have shown the association between *H. pylori* and iron deficiency anemia [65, 66]. According to the First World Congress of Pediatric Gastroenterology, Hepatology and Nutrition working group report, children with *H. pylori* infection have lower iron stores than healthy age-matched controls [67].

A study from Latin America showed that the levels of serum hemoglobin and ferritin were lower in children with *H. pylori* infection [68]. Harris et al. suggested that hypochlorhydria in children infected with *H. pylori* may be the key role in iron deficiency [69]. Furthermore, many studies have presented that the eradication of *H. pylori* in children with refractory anemia improved the hematological parameters in the short term [70]. In fact, it is difficult to differentiate between anemia associated with *H. pylori* infection and some other factors, such as nutritional status, poverty, and poor treatment [71, 72].

Growth faltering

Some studies have shown that *H. pylori* infection is associated with growth disorders in childhood [73, 74]. The infection is thought to reduce appetite, resulting in a decline in growth, short stature, decreased immunity, and recurrent infections [75–77]. Several studies showed that levels of ghrelin and leptin decreased in infected children with *H. pylori* and eradication of the infection led to positive effects on the growth parameters [78, 79]. While, Ozen et al. noted that among the biochemical parameters of growth, only the level of ghrelin was associated with *H. pylori* infection.

Bronchial asthma and allergy

According to some evidence, there is an inverse correlation between *H. pylori* seropositivity and asthma, but some other studies do not support these data. A meta-analysis of eight studies in a total of 14,972 participants by Wang et al. showed that there was weak evidence of an inverse relationship between asthma and *H. pylori* in children [80]. Karimi et al. in a cross-sectional study compared the prevalence of *H. pylori* infection in 98 patients with asthma and the same number of healthy children. This study showed that *H. pylori* infection do not play an important role in asthma [81]. Study by Chen and Blaser analyzed of data from a total of 7412 children participating in the National Nutrition and Nutrition Survey (NHANES) in the USA showed that *H. pylori* positivity was inversely related to dermatitis, asthma, allergic rhinitis, and eczema [82].

Diagnostic methods of *H. pylori* infection

Non-invasive tests

According to the topics discussed above, applying endoscopy test in children is not recommended, because of children who do not have the necessary cooperation. For this reason, non-invasive diagnostic tests with acceptable accuracy have been considered as; UBT, SAT, serology.

Urea breath test

Urea breath test is a reliable and non-invasive technique which does not need an endoscopy [15, 16]. Recommendations from the evidence-based guidelines emphasize that the UBT is a dependable and valuable method to determine whether or not the pathogen has been eradicated. Accordingly, this test is preferred over many other non-invasive tests including a stool antigen test to diagnose the effectiveness of treatment, although some studies have shown that UBT cannot confirm the presence of gastritis, esophageal pathologies, and ulcers [83]. UBT shows high sensitivity and specificity in *H. pylori* diagnosis. The sensitivity and specificity of this method in young children was found to be 95–97% and 97–98%, respectively [84–86]. However, some studies have suggested that the accuracy of this method is lower in children under the age of 6 years [87, 88]. Despite the fact that, UBT has high sensitivity and specificity, the accuracy of UBT in pediatrics is less than that of adults [15, 16]. To perform this test, isotypically labeled urea (^{12} C, ^{13}C, or ^{14}C) is administered into the patient and bacterial urease produced by *H. pylori* into the stomach will be measured. If the urease enzyme is present in the stomach, the urea is broken down into carbon dioxide and ammonia. CO2 reflects the flow of blood and exhale and can be measured with a mass spectrometer [84, 85]. The production of CO2 varies according to age, gender, and body weight [84, 89–91]. The isotopic ratio of labeled ^{13}CO2 or ^{14}CO2 may be higher in young children compared to adults, leading to low specificity and high false-positive findings in young children. The presence of urease-producing bacteria in the oral cavity of young children, such as *Klebsiella pneumonia* and *Proteus mirabilis*, may also cause false-positive results [92]. Prior treatment with antibiotics or proton pump inhibitors (PPIs) may cause false negatives. It is advisable to stop using

antibiotics for at least 4 weeks or proton pump inhibitors for at least 2 weeks prior to testing [15, 93].

Stool antigen test

The *H. pylori* stool antigen test is a non-invasive, easy, and cost-effective method that can be used for the clinical and epidemiological studies [83, 94]. The method offers advantages such as easy sampling of stool, easily transportability, and also a long-term storage capacity of these specimens in the frozen and even at the laboratory temperature [95–98]. The major disadvantage of the SAT is the lack of enthusiasm for patients in the stool sample preparation. In addition, storage may become a problem in areas where freezing is not available. There are two types of SAT methods developed for detecting *H. pylori* antigens in the stool. These are enzyme immunoassay (EIA) and immunochromatography assay (ICA)-based methods and utilize either polyclonal or monoclonal antibodies [41, 99, 100]. Although both monoclonal and polyclonal antibodies can be used in this method, monoclonal antibodies showed a higher sensitivity than another one mainly because of the difficulty in obtaining polyclonal antibodies of consistent quality every time [101]. Several studies have shown that acceptable accuracy of this test, particularly in EIA with monoclonal antibodies, thus such tests, especially with the use of monoclonal antibodies, are useful tools in the initial diagnosis and eradication assessment of *H. pylori* infection in all ages [102].

Studies of the performance of stool antigen testing in children have not shown differences by age, acute bleeding, and prior use of proton pump inhibitors [103–105]. Sensitivity and specificity have been similar in children of different age groups [106–108]. It should be noted that the sensitivity and specificity of the stool antigen test depend on some aspects as the cut-off value and treatment conditions [17, 109].

Serology

H. pylori infection causes immunological responses and antibody productions (IgA, IgG, and IgM) [15]. So that, IgM is detected in the initial steps of infection and IgA and IgG are detected in the chronic phase of *H. pylori* infection by ELISA, immunoblotting, and enzyme immunoassays (EIA). Samples such as serum, saliva, or urine can be used to detect the antibodies. Generally, antibody testing (IgA and IgM) may cause high false positives and is not trusted to confirm the presence of bacteria in the serum [110]. Thus serological testing is used as an initial screening test and the results will be confirmed with another test with high specificity. On the other hand, due to the continued presence of antibodies, especially IgG after the eradication of the organism for a long time, serological testing cannot be used for investigation the success of eradication treatment [111]. Moreover, the mean antibody levels in young children are lower than in older and adults leading to poor sensitivity of serological tests in children (63 to 86%) [72, 111–114]. Therefore, among non-invasive tests, serology is unreliable in young children an even any age groups [115, 116].

Invasive tests

Invasive tests are considered as the gold standard for detection of *H. pylori* infection in both children and adults due to their high diagnostic accuracy in comparison to non-invasive methods. The lack of a single method that offers full sensitivity and specificity is a major issue of any non-invasive method for the diagnosis of *H. pylori* in children [72]. However, non-invasive methods are most routinely used methods for *H. pylori* as they offer advantages of convenience and faster diagnosis, but fail to provide complementary information on the location of the *H. pylori* in the stomach [111].

Guidelines from North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommended for *H. pylori* testing in the patients with first-degree relatives for gastric cancer and refractory iron deficiency anemia without a well-known reason [17]. Both NASPGHAN and ESPGHAN has recommended that early detection of the presence of *H. pylori* be based on some invasive methods such as RUT, histology, and cultures. All these invasive methods requires prior endoscopy and gastric biopsy for sample collection [17, 117]. According to the guidelines, it is reasonable to diagnose *H. pylori* infection in children if that both histology and RUT were positive or even culture became positive alone. However, if the results of histology and RUT were not consistent, the non-invasive tests such as *H. pylori* stool antigen (HpSA) assay or UBT must be essential for diagnosis [117].

Histology

The histological examination provides a comprehensive assessment of gastric mucosa and thus aid in accurate diagnosis. To achieve highest possible diagnostic accuracy, it is recommended to obtain biopsy samples from multiple locations in the stomach due to the wide distributions of bacteria. Hematoxylin and Eosin (H & E) is the standard, special and routine stain for detection of inflammation and *H. pylori* [27]. Albeit in low densities of bacterial populations, special stains as silver stain are used to identify pathogens. It should be noted that Hematoxylin and Eosin staining is expensive [17, 118]. So, alternatives such as giemsa stains that are cheap, simple, sensitive, and specific for the detection of *H. pylori* is also commonly used [62, 119].

The major benefit of the histological examination is direct observation of the pathological changes associated with

H. pylori infection consisting of the grade of atrophy, inflammation rates, the involvement of gastric intestinal metaplasia (IM) and malignancy [118, 119]. The disadvantages of this method are not many, but include expensive, needing a lot of skill to do the test, and reduced sensitivity and specificity due to prior administration of several types of drugs such as antibiotics and PPIs.

Generally, the biopsy-based tests as histology is not applied in children or less recommended, because of the biopsy is difficult to perform in children, except for antibiotic resistance testing or if there are clear clinical indications for endoscopy in the child [62].

Rapid urease test

The performance basis of RUT test is the ability of *H. pylori* to produce urease enzyme to break down urea to carbon dioxide and ammonia [27, 120]. To perform the test, the biopsy sample will be transferred to a solution-containing urea (KH2PO4, NaCl, NaoH) with a PH indicator [87, 121, 122]. If the bacteria is present in the gastric mucosal biopsy samples, the hydrolysis of urea to ammonium raises the pH and the color of the solution change from yellow-gold to pink-red eventually [87, 121, 122]. Some oropharynx microbiota such as *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Citrobacter freundii*, and *Staphylococcus aureus* also produce urease; however, there will be no significant effect on the results of the test [120].

It has been stated in most studies that RUT should be done in children who have clinical symptoms but yet to administer any treatment [123]. The accuracy of RUT test depends on the number and location of the biopsies, the density of bacteria, recent intake of bismuth, antibiotics, PPIs, achlorhydria, and the prevalence rate of infection in the community [62, 120]. In biopsy samples, RUT is preferred for its quick results, easy availability, less expensive, and high sensitivity (about 80%) and specificity (within 100%) [15, 62].

Culture

The culture like the other invasive tests requires biopsy specimens obtained by endoscopy of the upper gastrointestinal tract [120]. This test as a gold standard is the only method that has 100% specificity. But its sensitivity varies depending on the expertise and experience of laboratory staff, culture media, and the quality of the sample [91, 111, 120, 124, 125]. The method is also expensive, time-consuming, and pose difficulties due to the specific nutritional requirements of *H. pylori* for cultures [27, 62]. The test is mainly limited in research to determine the antibiotic susceptibility of *H. pylori*. It should also be noted that results of culture may be affected by the prior use of antibiotics and PPIs [120, 121].

Polymerase chain reaction

The PCR tests could be classified as both invasive and non-invasive methods [7]. This method is accurate, trustworthy, fast, and affordable to detect *H. pylori* infection and used to detect genotypic bacterial identification, pathogenic and epidemiological studies, and antibiotic resistance as clarithromycin and fluoroquinolones [120, 126–129].

PCR can be performed on samples from biopsy, gastric juice, and stool [7, 130]. Several studies have shown that PCR test for the diagnosis of infection in children has an acceptable sensitivity in comparison to other tests. PCR test can detect very small amounts of DNA and thus can detect the presence of *H. pylori* even at a low bacterial load [130, 131]. Another advantage of PCR is the acceptable sensitivity of this test for diagnosis in the recipients of PPIs [132, 133].

One of the major problems for this test is the detection of *H. pylori* DNA even in dead bacterial samples leading to false positives.

Conclusion

Early diagnosis and treatment of acute *Helicobacter pylori* infection in children can reduce the incidence of various cancers and gastric ulcers in the future. Therefore, the clinicians should be alert to the importance of reaching a timely diagnosis of *H. pylori* infection. A powerful and standard diagnostic approach for diagnosis of *H. pylori* in children is being widely discussed. It is necessary to mention that the diagnosis of *H. pylori* infection in pediatric patients differs from that of adults. Invasive methods are not usually used clinically for children. Any invasive or even non-invasive tests that require patient collaboration are not easy for children. UBT and SAT are reliable, validated, and documented non-invasive methods for early detection and monitoring *H. pylori* infection after eradication. The choice of a diagnostic test for children should be based on the accuracy of the method, ability to performance, availability, cost-effectiveness, and clinical status of the patient.

Acknowledgments The authors express their appreciation to Vice Chancellor for Research and Technology of Babol University of Medical Sciences for supporting this research and Marzieh Nourollahzadeh for her advice as a translator of this article.

Specific author contributions P.S and S.E conceived the study; M.J, V.K, V.K.R.V, and S.E collected all data; P.S and S.E drafted the manuscript; and all authors commented on the drafts of the manuscript and approved the final draft of the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study received the approval from the Babol University of Medical Science, Ethical Committee.

Informed consent There is no informed consent for this review article.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Warren JR, Marshall B (1983) Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 321(8336):1273–1275
2. Marshall B, Warren JR (1984) Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 323(8390):1311–1315
3. Ebrahimpour S, Esmaeili H, Ghadimi R (2017) Food bioactive componts, a possible adjuvant for H. pylori eradication. Caspian J Intern Med 8(2):131
4. Suerbaum S, Michetti P (2002) Helicobacter pylori infection. N Engl J Med 347(15):1175–1186
5. Ohata H, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, Yoshikawa A, Yanaoka K, Arii K, Tamai H (2004) Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer. Int J Cancer 109(1):138–143
6. Hill R, Pearman J, Worthy P, Caruso V, Goodwin S, Blincow E (1986) Campylobacter pyloridis and gastritis in children. Lancet 327(8477):387
7. Sabbagh P, Mohammadnia-Afrouzi M, Javanian M, Babazadeh A, Koppolu V, Vasigala VR, Nouri HR, Ebrahimpour S (2018) Diagnostic methods for Helicobacter pylori infection: ideals, options, and limitations. J Clin Microbiol Infect Dis 38(1):55–66
8. Nejati S, Karkhah A, Darvish H, Validi M, Ebarhimpour S, Nouri HR (2018) Influence of Helicobacter pylori virulence factors CagA and VacA on pathogenesis of gastrointestinal disorders. Microb Pathog117:43–48
9. Tokudome S, Hosono A, Suzuki S, Ghadimi R, Tanaka T, Ichikawa H, Miyata M, Marumoto M, Agawa H, Arakawa K, Ando R, Hattori N, Shibata K, Yang Z (2006) Helicobacter pylori infection as an essential factor for stomach cancer. Asian Pac J Cancer Prev 7(1):163
10. Ernst PB, Gold BD (1999) Helicobacter pylori in childhood: new insights into the immunopathogenesis of gastric disease and implications for managing infection in children. J Pediatr Gastroenterol Nutr 28(5):462–473
11. Kusters JG, van Vliet AH, Kuipers EJ (2006) Pathogenesis of Helicobacter pylori infection. Clin Microbiol Rev 19(3):449–490
12. Correa P, Piazuelo MB (2008) Natural history of Helicobacter pylori infection. Dig Liver Dis 40(7):490–496
13. Imrie C, Rowland M, Bourke B, Drumm B (2001) Is Helicobacter pylori infection in childhood a risk factor for gastric cancer? Pediatrics 107(2):373–380
14. Sicinschi LA, Correa P, Bravo LE, Peek RM Jr, Wilson KT, Loh JT, Yepez MC, Gold BD, Thompson DT, Cover TL (2012) Noninvasive genotyping of Helicobacter pylori cagA, vacA, and hopQ from asymptomatic children. Helicobacter 17(2):96–106
15. Czinn SJ (2005) Helicobacter pylori infection: detection, investigation, and management. J Pediatr 146(3):S21–S26
16. Ou Z, Xiong L, Li D-Y, Geng L, Li L, Chen P, Yang M, Zeng Y, Zhou Z, Xia H (2013) Evaluation of a new fluorescence quantitative PCR test for diagnosing Helicobacter pylori infection in children. BMC Gastroenterol 13(1):7
17. Koletzko S, Jones NL, Goodman KJ, Gold B, Rowland M, Cadranel S, Chong S, Colletti RB, Casswall T, Elitsur Y (2011) Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr 53(2):230–243
18. Karkhah A, Ebrahimpour S, Rostamtabar M, Koppolu V, Darvish S, Vasigala VKR, Validi M, Nouri HR (2018) Helicobacter pylori evasion strategies of the host innate and adaptive immune responses to survive and develop gastrointestinal disease. Microbiol Res 218:49–57
19. Austin J, Doig P, Stewart M (1992) Structural comparison of urease and a GroEL analog from Helicobacter pylori. J Bacteriol 174(22):7470–7473
20. Amieva MR, El-Omar EM (2008) Host-bacterial interactions in Helicobacter pylori infection. Gastroenterology 134(1):306–323
21. Leunk R, Johnson P, David B, Kraft W, Morgan D (1988) Cytotoxic activity in broth-culture filtrates of Campylobacter pylori. J Med Microbiol 26(2):93–99
22. Willhite DC, Blanke SR (2004) Helicobacter pylori vacuolating cytotoxin enters cells, localizes to the mitochondria, and induces mitochondrial membrane permeability changes correlated to toxin channel activity. Cell Microbiol 6(2):143–154
23. Yamasaki E, Wada A, Kumatori A, Nakagawa I, Funao J, Nakayama M, Hisatsune J, Kimura M, Moss J, Hirayama T (2006) Helicobacter pylori vacuolating cytotoxin induces activation of the proapoptotic protein Bax and Bak, leading to cytochrome c release and cell death, independent of. J Biol Chem 281(16):11250–11259
24. Noto JM, Peek RM (2012) Helicobacter pylori: an overview. Helicobacter species. Springer, pp 7–10
25. Cadamuro ACT, Rossi AFT, Maniezzo NM, Silva AE (2014) Helicobacter pylori infection: host immune response, implications on gene expression and microRNAs. World J Gastroenterol: WJG 20(6):1424
26. Larussa T, Leone I, Suraci E, Imeneo M, Luzza F (2015) Helicobacter pylori and T helper cells: mechanisms of immune escape and tolerance. J Immunol Res 2015:981328–981328
27. Rajindrajith S, Devanarayana NM, De Silva HJ (2009) Helicobacter pylori infection in children. Saudi J Gastroenterol 15(2):86
28. Bellack N, Koehoorn M, MacNab Y, Morshed M (2006) A conceptual model of water's role as a reservoir in Helicobacter pylori transmission: a review of the evidence. Epidemiol Infect 134(3):439–449
29. Dube C, Nkosi T, Clarke A, Mkwetshana N, Green E, Ndip R (2009) Helicobacter pylori antigenemia in an asymptomatic population of Eastern Cape Province, South Africa: public health implications. Rev Environ Health 24(3):249–255
30. Konno M, S-i Y, Suga T, Takahashi M, Sato K, Fujii N (2008) Predominance of mother-to-child transmission of Helicobacter pylori infection detected by random amplified polymorphic DNA fingerprinting analysis in Japanese families. Pediatr Infect Dis J 27(11):999–1003
31. Weyermann M, Rothenbacher D, Brenner H (2009) Acquisition of Helicobacter pylori infection in early childhood: independent contributions of infected mothers, fathers, and siblings. Am J Gastroenterol 104(1):182
32. Zabala Torrres B, Lucero Y, Lagomarcino AJ, Orellana-Manzano A, George S, Torres JP, O'ryan M (2017) Prevalence and dynamics of Helicobacter pylori infection during childhood. Helicobacter 22(5):e12399
33. Opekun AR, Gilger MA, Denyes SM, Nirken MH, Philip SP, Osato MS, Malaty HM, Hicks J, Graham DY (2000) Helicobacter pylori infection in children of Texas. J Pediatr Gastroenterol Nutr 31(4):405–410

34. Wizla-Derambure N, Michaud L, Ategbo S, Vincent P, Ganga-Zandzou S, Turck D, Gottrand F (2001) Familial and community environmental risk factors for Helicobacter pylori infection in children and adolescents. J Pediatr Gastroenterol Nutr 33(1):58–63
35. Mourad-Baars PE, Verspaget HW, Mertens BJ, Mearin ML (2007) Low prevalence of Helicobacter pylori infection in young children in the Netherlands. Eur J Gastroenterol Hepatol 19(3):213–216
36. Bureš J, Kopáčová M, Koupil I, Seifert B, Fendrichová MŠ, Špirková J, Voříšek V, Rejchrt S, Douda T, Král N (2012) Significant decrease in prevalence of Helicobacter pylori in the Czech Republic. World J Gastroenterol: WJG 18(32):4412
37. Jafri W, Yakoob J, Abid S, Siddiqui S, Awan S, Nizami S (2010) Helicobacter pylori infection in children: population-based age-specific prevalence and risk factors in a developing country. Acta Paediatr 99(2):279–282
38. Poddar U, Yachha SK (2007) Helicobacter pylori in children: an Indian perspectiveIndian Pediatr 44(10):761–770
39. Naous A, Al-Tannir M, Naja Z, Ziade F, El-Rajab M (2007) Fecoprevalence and determinants of Helicobacter pylori infection among asymptomatic children in Lebanon. J Med Liban 55(3): 138–144
40. Mohammad MA, Hussein L, Coward A, Jackson SJ (2008) Prevalence of Helicobacter pylori infection among Egyptian children: impact of social background and effect on growth. Public Health Nutr 11(3):230–236
41. Sýkora J, Siala K, Varvařovská J, Pazdiora P, Pomahačová R, Huml M (2009) Epidemiology of Helicobacter pylori infection in asymptomatic children: a prospective population-based study from the Czech Republic. Application of a monoclonal-based antigen-in-stool enzyme immunoassay. Helicobacter 14(4):286–297
42. Staat MA, Kruszon-Moran D, McQuillan GM, Kaslow RA (1996) A population-based serologic survey of Helicobacter pylori infection in children and adolescents in the United States. J Infect Dis 174(5):1120–1123
43. Patterson T, Straten E, Jimenez S (2012) The prevalence of Helicobacter pylori antibody in different age groups in Central Texas. Clin Lab Sci 25(2):102
44. Tkachenko MA, Zhannat NZ, Erman LV, Blashenkova EL, Isachenko SV, Isachenko OB, Graham DY, Malaty HM (2007) Dramatic changes in the prevalence of Helicobacter pylori infection during childhood: a 10-year follow-up study in Russia. J Pediatr Gastroenterol Nutr 45(4):428–432
45. Fock KM, Ang TL (2010) Epidemiology of Helicobacter pylori infection and gastric cancer in Asia. J Gastroenterol Hepatol 25(3): 479–486
46. De Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M (2012) Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 13(6): 607–615
47. Sachs G, Scott DR (2012) Helicobacter pylori: eradication or preservation. F1000 Med Rep 4:7
48. Frank F, Stricker T, Stallmach T, Braegger CP (2000) Helicobacter pylori infection in recurrent abdominal pain. J Pediatr Gastroenterol Nutr 31(4):424–427
49. Kimia A, Zahavi I, Shapiro R, Rosenbach Y, Hirsh A, Druzd T, Yahav J, Dinari G (2000) The role of Helicobacter pylori and gastritis in children with recurrent abdominal pain. Isr Med Assoc J 2(2):126–128
50. Masoodpoor N, Sheikhvatan M (2010) Helicobacter pylori infection in Iranian children with recurrent abdominal pain. Trop Gastroenterol 29(4):221–223
51. Spee LA, Madderom MB, Pijpers M, van Leeuwen Y, Berger MY (2010) Association between Helicobacter pylori and gastrointestinal symptoms in children. Pediatrics 125(3):e651–e669
52. Moon A, Solomon A, Beneck D, Cunningham-Rundles S (2009) Positive association between Helicobacter pylori and gastroesophageal reflux disease in children. J Pediatr Gastroenterol Nutr 49(3): 283
53. Emiroglu HH, Sokucu S, Suoglu OD, Gulluoglu M, Gokce S (2010) Is there a relationship between Helicobacter pylori infection and erosive reflux disease in children? Acta Paediatr 99(1): 121–125
54. Daugule I, Rumba I, Alksnis J, Ejderhamn J (2007) Helicobacter pylori infection among children with gastrointestinal symptoms: a high prevalence of infection among patients with reflux oesophagitis. Acta Paediatr 96(7):1047–1049
55. Ierardi E, Giangaspero A, Losurdo G, Giorgio F, Amoruso A, De V (2014) Quadruple rescue erapy after first and second line failure for Helicobacter pylori treatment: comparison between two tetracycline-based regimens. J Gastrointestin Liver Dis 23(4): 367–370
56. Wu J, Chan F, Ching J, Leung W, Hui Y, Leong R, Chung S, Sung J (2004) Effect of Helicobacter pylori eradication on treatment of gastro-oesophageal reflux disease: a double blind, placebo controlled, randomised trial. Gut 53(2):174–179
57. Wu J, Chan F, Wong S, Lee Y, Leung W, Sung J (2002) Effect of Helicobacter pylori eradication on oesophageal acid exposure in patients with reflux oesophagitis. Aliment Pharmacol Ther 16(3): 545–552
58. Gold BD (2003) Outcomes of pediatric gastroesophageal reflux disease: in the first year of life, in childhood, and in adults... oh, and should we really leave Helicobacter pylori alone? J Pediatr Gastroenterol Nutr 37:S33–S39
59. Masrour-Roudsari J, Ebrahimpour S (2017) Causal role of infectious agents in cancer: an overview. Caspian J Intern Med 8(3): 153–158
60. Nourollahpour Shiadeh M, Riahi SM, Adam I, Saber V, Behboodi Moghadam Z, Armon B, Spotin A, Nazari Kangavari H, Rostami A (2019) Helicobacter pylori infection and risk of preeclampsia: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 32(2):324–331
61. Kim SS, Ruiz VE, Carroll JD, Moss SF (2011) Helicobacter pylori in the pathogenesis of gastric cancer and gastric lymphoma. Cancer Lett 305(2):228–238
62. Rowland M, Bourke B, Drumm B (2004) Helicobacter pylori and peptic ulcer disease. Pediatric gastrointestinal disease, 4th edn. BC Decker Co., Canada, pp 491–505
63. Macarthur C, Saunders N, Feldman W (1995) Helicobacter pylori, gastroduodenal disease, and recurrent abdominal pain in children. Jama 273(9):729–734
64. Yeung C-Y, Lee H-C (2017) Paediatric Helicobacter pylori infection in Taiwan: current status and perspectives. Gastroenterology 6(1):90–97
65. Choi J (2003) Does Helicobacter pylori infection relate to iron deficiency anaemia in prepubescent children under 12 years of age? Acta Paediatr 92(8):970–972
66. Choe Y, Kim S, Hong Y (2003) The relationship between Helicobacter pylori infection and iron deficiency: seroprevalence study in 937 pubescent children. Arch Dis Child 88(2):178–178
67. Sherman P, Czinn S, Drumm B, Gottrand F, Kawakami E, Madrazo A, Oderda G, Seo J-K, Sullivan P, Toyoda S (2002) Helicobacter pylori infection in children and adolescents: working group report of the first world congress of pediatric gastroenterology, hepatology, and nutrition. J Pediatr Gastroenterol Nutr 35: S128–S133
68. Queiroz DMM, Harris PR, Sanderson IR, Windle HJ, Walker MM, Rocha AMC, Rocha GA, Carvalho SD, Bittencourt PFS, de Castro LPF (2013) Iron status and Helicobacter pylori infection in symptomatic children: an international multi-centered study. PLoS One 8(7):e68833

69. Harris PR, Serrano CA, Villagrán A, Walker MM, Thomson M, Duarte I, Windle HJ, Crabtree JE (2013) Helicobacter pylori-associated hypochlorhydria in children, and development of iron deficiency. J Clin Pathol 66(4):343–347
70. Cardenas VM, Prieto-Jimenez CA, Mulla ZD, Rivera JO, Dominguez DC, Graham DY, Ortiz M (2011) Helicobacter pylori eradication and change in markers of iron stores among non–iron-deficient children in El Paso, Texas: an etiologic intervention study. J Pediatr Gastroenterol Nutr 52(3):326–332
71. Homan M, Hojsak I, Kolaček S (2012) Helicobacter pylori in pediatrics. Helicobacter 17:43–48
72. Kindermann A, Lopes AI (2009) Helicobacter pylori infection in pediatrics. Helicobacter 14:52–57
73. Thomas J, Dale A, Bunn J, Harding M, Coward W, Cole T, Weaver L (2004) Early Helicobacter pylori colonisation: the association with growth faltering in the Gambia. Arch Dis Child 89(12):1149–1154
74. Mera RM, Correa P, Fontham EE, Reina JC, Pradilla A, Alzate A, Bravo LE (2006) Effects of a new Helicobacter pylori infection on height and weight in Colombian children. Ann Epidemiol 16(5): 347–351
75. Prentice A, Darboe M (2008) Growth and host-pathogen interactions. The window of opportunity: pre-pregnancy to 24 months of age. Karger Publishers 61:197–210
76. Soylu ÖB, Ozturk Y (2008) Helicobacter pylori infection: effect on malnutrition and growth failure in dyspeptic children. Eur J Pediatr 167(5):557–562
77. Cherian S, Forbes D, Sanfilippo F, Cook A, Burgner D (2009) Helicobacter pylori, helminth infections and growth: a cross-sectional study in a high prevalence population. Acta Paediatr 98(5):860–864
78. Ozen A, Furman A, Berber M, Karatepe HO, Mutlu N, Sarıçoban HE, Büyükgebiz B (2011) The effect of Helicobacter pylori and economic status on growth parameters and leptin, ghrelin, and insulin-like growth factor (IGF)-I concentrations in children. Helicobacter 16(1):55–65
79. Yang Y-J, Sheu B-S, Yang H-B, Lu C-C, Chuang C-C (2012) Eradication of Helicobacter pylori increases childhood growth and serum acylated ghrelin levels. World J Gastroenterol: WJG 18(21):2674
80. Wang Y, Bi Y, Zhang L, Wang C (2012) Is Helicobacter pylori infection associated with asthma risk? A meta-analysis based on 770 cases and 785 controls. Int J Med Sci 9(7):603
81. Karimi A, Fakhimi-Derakhshan K, Imanzadeh F, Rezaei M, Cavoshzadeh Z, Maham S (2013) Helicobacter pylori infection and pediatric asthma. Iran J Microbiol 5(2):132
82. Chen Y, Blaser MJ (2008) Helicobacter pylori colonization is inversely associated with childhood asthma. J Infect Dis 198(4): 553–560
83. Ertem D (2013) Clinical practice: Helicobacter pylori infection in childhood. Eur J Pediatr 172(11):1427–1434
84. Kawakami E, Machado RS, Reber M, Patrício FRS (2002) 13C-urea breath test with infrared spectroscopy for diagnosing Helicobacter pylori infection in children and adolescents. J Pediatr Gastroenterol Nutr 35(1):39–43
85. Megraud F (2005) On behalf of the European pediatric task force on Helicobacter pylori comparison of non-invasive tests to detect Helicobacter pylori infection in children and adolescents results of a multicenter European study. J Pediatr 146:198–203
86. Leal YA, Flores LL, Fuentes-Pananá EM, Cedillo-Rivera R, Torres J (2011) 13C-urea breath test for the diagnosis of Helicobacter pylori infection in children: a systematic review and meta-analysis. Helicobacter 16(4):327–337
87. Drumm B, Koletzko S, Oderda G, pylori EPTFoH (2000) Helicobacter pylori infection in children: a consensus statement. J Pediatr Gastroenterol Nutr 30(2):207–213
88. Pathak C, Bhasin D, Khanduja K (2004) Urea breath test for Helicobacter pylori detection: present status. Trop Gastroenterol 25(4):156–161
89. Delvin EE, Brazier JL, Deslandres C, Alvarez F, Russo P, Seidman E (1999) Accuracy of the [13C]-urea breath test in diagnosing Helicobacter pylori gastritis in pediatric patients. J Pediatr Gastroenterol Nutr 28(1):59–62
90. Kato S, Ozawa K, Konno M, Tajiri H, Yoshimura N, Shimizu T, Fujisawa T, Abukawa D, Minoura T, Iinuma K (2002) Diagnostic accuracy of the 13 C-urea breath test for childhood Helicobacter pylori infection: a multicenter Japanese study. Am J Gastroenterol 97(7):1668
91. Ogata SK, Kawakami E, Patrício FRS, Pedroso MZ, Santos AM (2001) Evaluation of invasive and non-invasive methods for the diagnosis of Helicobacter pylori infection in symptomatic children and adolescents. Sao Paulo Med J 119(2):67–71
92. Jones NL, Sherman PM (2001) Approaching Helicobacter pylori infection in children: level I evidence at last and a word of caution. J Pediatr 139(5):622–623
93. Canete A, Abunají Y, Alvarez-Calatayud G, DeVicente M, González-Holguera JA, Leralta M, Pajares JM, Gisbert JP (2003) Breath test using a single 50-mg dose of 13C-urea to detect Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr 36(1):105–111
94. Elitsur Y, Yahav J (2005) Helicobacter pylori infection in pediatrics. Helicobacter 10:47–53
95. Koletzko S, Konstantopoulos N, Bosman D, Feydt-Schmidt A, Van der Ende A, Kalach N, Raymond J, Rüssmann H (2003) Evaluation of a novel monoclonal enzyme immunoassay for detection of Helicobacter pylori antigen in stool from children. Gut 52(6):804–806
96. Roggero P, Bonfiglio A, Luzzani S, Valadè A, Cataliotti E, Corno G, Garlaschi MC, Carissimi E, Mosca F, Carnelli V (2002) Helicobacter pylori stool antigen test: a method to confirm eradication in children. J Pediatr 140(6):775–777
97. van Doorn OJ, Bosman DK, van't Hoff BW, Taminiau JA, Fibo J, van der Ende A (2001) Helicobacter pylori stool antigen test: a reliable non-invasive test for the diagnosis of Helicobacter pylori infection in children. Eur J Gastroenterol Hepatol 13(9):1061–1065
98. Yee Y, Yip K, Que T, Chang K, Li K, Lee C, Wong S, Lau S, Szeto M (2002) Efficacy of enzyme immunoassay for the detection of Helicobacter pylori antigens in frozen stool specimens: local validation. Aliment Pharmacol Ther 16(10):1739–1742
99. Raguza D, Machado RS, Ogata SK, Granato CFH, Patrício FRS, Kawakami E (2010) Validation of a monoclonal stool antigen test for diagnosing Helicobacter pylori infection in young children. J Pediatr Gastroenterol Nutr 50(4):400–403
100. Wu D-C, Wu I-C, Wang S-W, Lu C-Y, Ke H-L, Yuan S-SF, Wang Y-Y, Chang W-H, Wang T-E, Bair M-J (2006) Comparison of stool enzyme immunoassay and immunochromatographic method for detecting Helicobacter pylori antigens before and after eradication. Diagn Microbiol Infect Dis 56(4):373–378
101. Makristathis A, Barousch W, Pasching E, Binder C, Kuderna C, Apfalter P, Rotter ML, Hirschl AM (2000) Two enzyme immunoassays and PCR for detection ofHelicobacter pylori in stool specimens from pediatric patients before and after eradication therapy. J Clin Microbiol 38(10):3710–3714
102. Crone J, Gold BD (2004) Helicobacter pylori infection in pediatrics. Helicobacter 9:49–56
103. Asfeldt A, Løchen M-L, Straume B, Steigen S, Florholmen J, Goll R, Nestegard O, Paulssen E (2004) Accuracy of a monoclonal antibody-based stool antigen test in the diagnosis of Helicobacter pylori infection. Scand J Gastroenterol 39(11):1073–1077
104. Gatta L, Vakil N, Ricci C, Osborn JF, Tampieri A, Perna F, Miglioli M, Vaira D (2004) Effect of proton pump inhibitors and

antacid therapy on 13 C urea breath tests and stool test for Helicobacter pylori infection. Am J Gastroenterol 99(5):823
105. Gisbert J, Trapero M, Calvet X, Mendoza J, Quesada M, Güell M, Pajares J (2004) Evaluation of three different tests for the detection of stool antigens to diagnose Helicobacter pylori infection in patients with upper gastrointestinal bleeding. Aliment Pharmacol Ther 19(8):923–929
106. Kuloğlu Z, Kansu A, Kırsaçlıoğlu CT, Üstündağ G, Aysev D, Ensari A, Küçük NÖ, Girgin N (2008) A rapid lateral flow stool antigen immunoassay and 14C-urea breath test for the diagnosis and eradication of Helicobacter pylori infection in children. Diagn Microbiol Infect Dis 62(4):351–356
107. Nares-Cisneros J, Jaramillo-Rodríguez Y, Martínez-Ordaz VA, Velasco-Rodríguez VM, Madero A, Mena-Arias G, Manriquez-Covarrubias L (2007) Immunochromatographic monoclonal test for detection of Helicobacter pylori antigen in stool is useful in children from high-prevalence developing country. Helicobacter 12(4):354–358
108. Yang HR, Seo JK (2008) Helicobacter pylori stool antigen (HpSA) tests in children before and after eradication therapy: comparison of rapid immunochromatographic assay and HpSA ELISA. Dig Dis Sci 53(8):2053–2058
109. Choi J, Kim CH, Kim D, Chung SJ, Song JH, Kang JM, Yang JI, Park MJ, Kim YS, Yim JY (2011) Prospective evaluation of a new stool antigen test for the detection of Helicobacter pylori, in comparison with histology, rapid urease test, 13C-urea breath test, and serology. J Gastroenterol Hepatol 26(6):1053–1059
110. Day AS, Sherman PM (2002) Accuracy of office-based immunoassays for the diagnosis of Helicobacter pylori infection in children. Helicobacter 7(3):205–209
111. Guarner J, Kalach N, Elitsur Y, Koletzko S (2010) Helicobacter pylori diagnostic tests in children: review of the literature from 1999 to 2009. Eur J Pediatr 169(1):15–25
112. Czinn SJ (1999) Serodiagnosis of Helicobacter pylori in pediatric patients. LWW
113. Daugule I, Rowland M (2008) Helicobacter pylori infection in children. Helicobacter 13:41–46
114. Westblom T, Madan E, Gudipati S, Midkiff B, Czinn S (1992) Diagnosis of Helicobacter pylori infection in adult and pediatric patients by using Pyloriset, a rapid latex agglutination test. J Clin Microbiol 30(1):96–98
115. Kato S, Nakayama K, Minoura T, Konno M, Tajiri H, Matsuhisa T, Iinuma K (2004) Comparison between the 13 C-urea breath test and stool antigen test for the diagnosis of childhood Helicobacter pylori infection. J Gastroenterol 39(11):1045–1050
116. Hino B, Eliakim R, Levine A, Sprecher H, Berkowitz D, Hartman C, Eshach-Adiv O, Shamir R (2004) Comparison of invasive and non-invasive tests diagnosis and monitoring of Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr 39(5):519–523
117. Thijs J, Van Zwet A, Thijs W, Oey H, Karrenbeld A, Stellaard F, Luijt D, Meyer B, Kleibeuker J (1996) Diagnostic tests for Helicobacter pylori: a prospective evaluation of their accuracy, without selecting a single test as the gold standard. Am J Gastroenterol 91(10):2125–2129
118. Dixon MF, Genta RM, Yardley JH, Correa P (1996) Classification and grading of gastritis: the updated Sydney system. Am J Surg Pathol 20(10):1161–1181
119. Malfertheiner P, Megraud F, O'morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T (2012) Management of Helicobacter pylori infection—the Maastricht IV/ Florence consensus report. Gut 61(5):646–664
120. Garza-González E, Perez-Perez GI, Maldonado-Garza HJ, Bosques-Padilla FJ (2014) A review of Helicobacter pylori diagnosis, treatment, and methods to detect eradication. World J Gastroenterol: WJG 20(6):1438
121. Gold BD, Colletti RB, Abbott M, Czinn SJ, Elitsur Y, Hassall E, Macarthur C, Snyder J, Sherman PM (2000) Helicobacter pylori infection in children: recommendations for diagnosis and treatment. J Pediatr Gastroenterol Nutr 31(5):490–497
122. Sabbi T, De Angelis P, Colistro F, Dall'Oglio L, di Abriola GF, Castro M (2005) Efficacy of noninvasive tests in the diagnosis of Helicobacter pylori infection in pediatric patients. Arch Pediatr Adolesc Med 159(3):238–241
123. Madani S, Rabah R, Tolia V (2000) Diagnosis of Helicobacter pylori infection from antral biopsies in pediatric patients: is urease test that reliable? Dig Dis Sci 45(6):1233–1237
124. Ni Y-H, Lin J-T, Huang S-F, Yang J-C, Chang M-H (2000) Accurate diagnosis Helicobacter pylori infection by stool antigen test and 6 other currently available tests in children. J Pediatr 136(6):823–827
125. Velapatino B, Balqui J, Gilman RH, Bussalleu A, Quino W, Finger SA, Santivanez L, Herrera P, Piscoya A, Valdivia J (2006) Validation of string test for diagnosis of Helicobacter pylori infections. J Clin Microbiol 44(3):976–980
126. Belda S, Saez J, Santibáñez M, Rodríguez JC, Galiana A, Sola-Vera J, Ruiz-García M, Brotons A, López-Girona E, Girona E (2012) Quantification of Helicobacter pylori in gastric mucosa by real-time polymerase chain reaction: comparison with traditional diagnostic methods. Diagn Microbiol Infect Dis 74(3): 248–252
127. Molnar B, Szoke D, Ruzsovics A, Tulassay Z (2008) Significantly elevated Helicobacter pylori density and different genotype distribution in erosions as compared with normal gastric biopsy specimen detected by quantitative real-time PCR. Eur J Gastroenterol Hepatol 20(4):305–313
128. Rimbara E, Sasatsu M, Graham DY (2013) PCR detection of Helicobacter pylori in clinical samples. Methods Mol Biol 943: 279–87
129. Duś I, Dobosz T, Manzin A, Loi G, Serra C, Radwan-Oczko M (2013) Role of PCR in Helicobacter pylori diagnostics and research--new approaches for study of coccoid and spiral forms of the bacteria. Postepy Hig Med Dosw (Online) 67(9):261–218
130. Kalach N, Gosset P, Dehecq E, Decoster A, Spyckerelle C, Papadopolos S, Dupont C, Raymond J (2015) Usefulness of gastric biopsy–based real-time polymerase chain reaction for the diagnosis of Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr 61(3):307–312
131. Chung WC, Jung SH, Oh JH, Kim TH, Cheung DY, Kim BW, Kim SS, Kim JI, Sin EY (2014) Dual-priming oligonucleotide-based multiplex PCR using tissue samples in rapid urease test in the detection of Helicobacter pylori infection. World J Gastroenterol: WJG 20(21):6547
132. Bazin T, Nchare Mfondi A, Julie C, Émile J-F, Raymond J, Lamarque D (2018) Contribution of genetic amplification by PCR for the diagnosis of Helicobacter pylori infection in patients receiving proton pump inhibitors. United European Gastroenterol J 6(8):1267–1273
133. Yakoob J, Jafri W, Abbas Z, Abid S, Islam M, Ahmed Z (2008) The diagnostic yield of various tests for Helicobacter pylori infection in patients on acid-reducing drugs. Dig Dis Sci 53(1):95–100