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'Gastroenterology in Pediatrics: Current knowledge about some common disorders'

Editor

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Helicobacter pylori infection in children

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REVIEW ARTICLE

Helicobacter pylori infection in children

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Abstract:
Helicobacter pylori infection is mainly acquired during childhood period. It is recognised as a cause of gastritis and peptic ulcer and it has been classified as a group A carcinogen by the World Health Organisation. There is emerging evidence in different populations including developing countries that the prevalence of H.pylori is declining in all age groups. Neither the treatment of the infection nor improvement in socioeconomic factors fully explains the decline. Most of the infected children are asymtomatic, and there is no specific clinical picture indicating a need to screen for H. pylori in pediatric age groups. Although there is abundance of invasive and non-invasive tests for the diagnosis of the infection, there is still no single noninvasive diagnostic test for the diagnosis of H.pylori in children, particularly in infants. Additionally, the real outcome of the infecion in children is still obscure. The scope of this review was to discuss the epidemiology, clinical features, diagnostic techniques, and management of H.pylori infection pediatric paitents.

Key words: *Helicobacter pylori, prevalence, abdominal pain, dyspesia, anemia, treatment*
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Introduction

Helicobacter pylori (H. pylori) is a gram-negative, spiral-shaped, flagellate bacterium, which naturally colonises humans by living in the gastric mucus, causes chronic active and chronic persistent gastritis in both adults and children. Infection is usually acquired during early childhood particularly in developing countries, and the prevalence of H. pylori gastritis increases with age in children (1). Low socio-economic background and their natural consequences, such as poor hygiene, overcrowding and insufficient sanitation, predispose to the acquisition of the bacterium. (2-8). The factors determining the subset of infected individuals developing disease as compared with those remaining as H. pylori carriers remain unclear. However, both host and bacterial factors contribute to differences in H. pylori pathogenicity. There are epidemiological data linking chronic H. pylori infection, probably beginning in childhood, with the development of gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma (9). The World Health Organisation's statement classifying H. pylori as a group 1 carcinogen could result in significant parental pressure for screening of children and treatment if H. pylori is found to

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TABLE 1. Most recent studies reporting prevalence of *Helicobacter pylori* infection in children.

Authors	Country, study population	Methods of sampling	Diagnositic test	Age range (yr)	Number of subjects	Number of *H.pylori* positive (%)
Acosta Garcia et al. 2009 (3)	Venezuela, healthy school children	random	^{13}C-UBT	4-14	231	**74**
Chi et al. 2009 (4)	Taiwan, healthy high-school students	not stated	^{13}C-UBT	mean 14.3	106	**55**
Dube et al. 2009 (5)	South Africa, healthy children and adults	not stated	Stool antigen testing	0-60	356	**87**
Jafri et al. 2010 (6)	Pakistan, children	cluster	Serum IgG antibodies	1-15	1976	**47**
Santos et al. 2009 (7)	Bolivia, healthy school children	random	^{13}C-UBT	5-8	424	**74**
	Cuba, healthy schoolchildren	random	^{13}C-UBT	6-14	996	**48**
	Venezuela, school children	intention sampling of schools	^{13}C-UBT	4-13	418	**78**
Sykora et al. 2009 (14)	Czech Republic, healthy children	random	Stool antijen	0-15	1545	**7**
Yucel et al. 2009 (16)	Turkey, healthy children	volunteered by parents	Stool antigen	2-12	165	**31**
Ertem et al. 2003 (7)	Turkey, healthy school children	random	^{13}C-UBT	3-12	327	**49.5**
Tam et al. 2008 (8)	Chinese, healthy children	random	^{13}C-UBT	6-19	2480	13.1

be present. Since there is no specific symptom pattern in H. pylori infected children, it has not been recommended to screen children with gastrointestinal symptoms and recurrent abdominal pain for the presence of H. pylori infection (10).

Epidemiology & Risk Factors

Approximately 65% of children in developing countries are infected with H. pylori at adolesence (11). Several studies regarding the epidemiology of H.pylori have reported that there is a positive association with household

density of children, low socioeconomic status, and poor sanitation (12,13). The human host remains the principal reservoir. Transmission occurs via person-to-person passage and unclean water sources have been implicated (13-15). Several studies have suggested that children acquire H. pylori strains most frequently from their mothers, hence infected mothers are the main independent source of H. pylori infection for their children (16,17). While there is a decline in the prevelance of H. pylori infection in Europa, the high prevalence in Asia and developing countries still persists (11,18,19). Literature search regarding the prevalence of H. pylori among healthy subjects by using different secreening methods is presented in table 1. Since different screening methods such as stool antigen test, serology and 13C-urea breath test (13C-UBT) were used in those studies, the prevalence rates varied according not only to the different geographical areas but also to the sensitivity of the test used to detect H. pylori infection. Prevalence of H. pylori infection varied between 7% in a study conducted among asymptomatic children in the Czech Republic (19), and 87% in South Africa (5). A cross-sectional population-based study of H. pylori prevalence was conducted on 2480 Chinese children (age 6–19 years) by using 13C-UBT, revealed a low prevalence rate of 13.1% (13). The major risk factors in this group were low educational level of the child's mother (OR = 2.43), family history of gastric cancer (OR = 2.19), and household crowding more than 5 (OR = 1.57). By using 13C-UBT , we studied the prevalence of H. pylori in 327 healthy Turkish school children (3-12 years old), and overall 49.5% of the children were found to be positive (12). In this study, it was shown that prevalence of the infection increased with age, and reached 63% at 11 years of age and older (Figure 1). Logistic regression analysis of the data revealed that lower socioeconomic status, household crowding of siblings and absence of breast feeding were independent risk factors for H. pylori infection. The same cohort was followed-up for 6 years and the incidence of H. pylori infection among previously uninfected children was 14%, and spontaneous loss of infection among previously infected children was 5.5% during this period (20). Hence, 2.5-fold higher rate of acquisition compared to the loss of infection suggested that spontaneous clearance of H. pylori infection has no significant role at least in a country with a high prevalence of H.pylori. However, more recently Yucel et al. (21) investigated 165 asymptomatic children aging between 2-12 years by using stool antigen test. The prevalence was 31% in these asymptomatic Turkish children, and when compared to the prevalence rates found in earlier studies in Turkey, there is a decline in prevalence of H. pylori in both children and adult population of our country (11). This is consitent with the decrease in the prevalence of H.pylori infection in different geographical areas over the last decade.

Most of the published studies regarding risk factors focused on socioeconomic indicators, and family income, household crowding, number of children sharing the same room, parents's education, sahring bed with children were identified as major risk factors associated with H.pylori infection (8,11-13). Today, it has become more evident that mothers as well as infected siblings serve as independent risk factors for childhood H. pylori infection (16,17). Cultural factors determine the child-rearing practices in different populations. It has been shown that peculiar eating habits such as sharing plates, glasses, and spoons, tasting food before feeding the child might be associated with

H.pylori infection particularly in countries with higher prevalance of the infection (2,8).

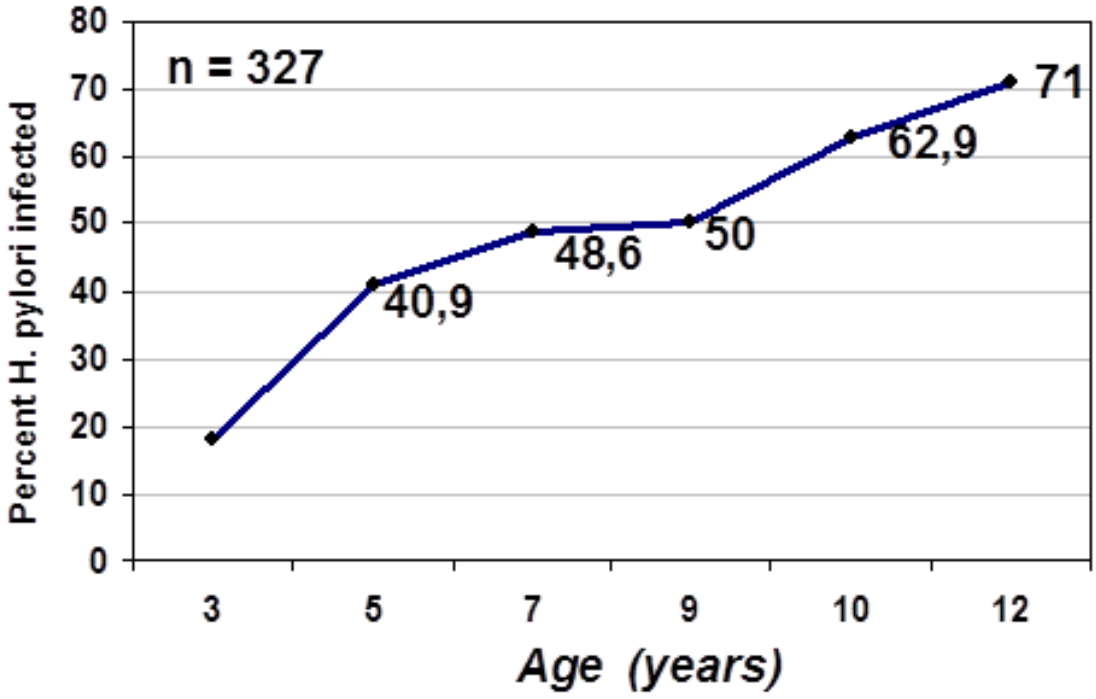

FIGURE 1. Prevalence of H. pylori among healthy Turkish school children (adapted from ref. 12).

Symptoms & clinical findings

It has been agreed that, there is no specific clinical picture indicating a need to screen for H. pylori in pediatric age groups. Although recurrent abdominal pain (RAP) is a frequent symptom (up to 15%) in school-age children, no association between RAP and H.pylori infection has been identified (22,23). Furthermore, most of the infected children are asymptomatic. It has been approved that children with RAP should not undergo non-invasive or endoscopy-based tests in order to seek evidence of H. pylori infection. Several consensus statements and guidelines (NASPGHAN and ESPGHAN) have suggested that children with abdominal pain should undergo investigations for H. pylori only in a situation in which upper endoscopy is performed to look for organic disease such as peptic ulcer or esophagitis (24,25). Although there is no specific symptom pattern in H. pylori-infected children, very recently, it has been shown that epigastric pain might be associated with H. pylori infection (23).

H. pylori infection is the most important cause of primary duodenal ulcers in children. In our tertiary center, a retrospective analysis of endoscopic procedures done over three years revealed a frequency of 9.4% peptic ulcer (88% primary peptic ulcer) in children who underwent endoscopy because of complicated recurrent abdominal/epigastric pain and gastric bleeding (26). Four out of 34 children with peptic ulcer had a history of recent use of NSAID. Two third of the ulcers were located in the duodenal bulb and 76% of the children with peptic ulcer were infected with H. pylori.

Epidemiological evidence has indicated that there is a link between gastric cancer and H. pylori infection; however, no study has shown that H. pylori eradication during childhood

prevents the development of gastric malignancies. The significance of H. pylori infection in children in terms of the risk of gastric cancer occurring in adult life requires further study, because it is likely to be a critical issue in determining whether widespread screening and treatment strategies are implemented among children (9,27,28). However, screening of children with a family history of gastric cancer is recommended if they are symptomatic.

Associated diseases (extragastrointestınal manifestations)

The role of H. pylori in dyspepsia and extradigestive diseases (vascular, immunological and skin pathologies and delayed statural growth) is still controversial (1,10). Children present an ideal model for studying the interaction between H. pylori and the gastric mucosa because a pediatric-age child is free from the common causes of secondary gastrointestinal diseases (drugs, smoking and alcohol). Furthermore, the natural history of diseases related to H. pylori is conditioned by the early acquisition of the bacterium.

Iron Deficiency Anemia: The association between H.pylori infection and iron deficiency anemia (IDA), has been the focus of attention more than one decade (29,30). Two main mechanisms have been proposed to explain the association between H. pylori infection and IDA. The first was diversion of iron away from the bone marrow in H. pylori infected patients with IDA and the second was that H.pylori associated pangastritis decreases gastric acidity which in turn decreases non-heme iron absorption (31,32). A very recent meta-analysis on observational studies suggested an association between H. pylori and IDA. In RCTs, eradication of H. pylori could also improve hemoglobin and serum ferritin levels to some extend (33). However, it is often difficult to distinguish between IDA due to H.pylori infection and to the other confounding factors such as poor nutritional status or another underlying disease. Hence, endoscopic examination may be indicated in children with refractory IDA in orderr to rule out not only the presence of H. pylori but also other causes of IDA such as malabsorption syndromes.

Growth Failure: Discussions about the possible association between H. pylori and growth retardation are ongoing. However, it has been argued that growth failure could be confounded by several other factors including lower socioeconomic status. There are some studies, mainly from developing countries, indicating an association between short stature and H.pylori infection (34-36). However, none of the studies to date has demonstrated a causal relationship between H.pylori and short stature by demonstrating an increase in growth velocity in children following eradication of H. pylori infection.

Allergy: It was postulated that allergic diseases were less common among H. pylori-infected individuals, whereas others proposed a greater susceptibility to atopy in H.pylori-infected population in population-based cross sectional or epidemiologic studies (37,38). In developed countries, allergies have become more prevalent in recent decades, whereas the prevalence of H.pylori has been decreasing in those countries. The mechanism proposed for this effect is that such infections may shift the balance of immune response towards the Th1, thereby reducing the expression of Th2 cytokines, principally associated with allergy (39). The interaction between H.pylori infection and atopy has been studied regarding the immunologic origin of these two counteractive conditions in order to elucidate the immunologic basis and the proposed inverse relationship between infections and atopic diseases (40). The frequency of atopy was lower in the H.pylori-

infected group (32% vs. 48%), whereas atopic symptoms were similar between infected and noninfected children. The results of this study demonstrated a counteractive Th1 and Th2 cytokine interaction between H.pylori infection and atopy, but it did not protect against atopy.

Diagnosis

H.pylori infection can be diagnosed by invasive techniques requiring endoscopy and biopsy such as histological examination, culture and a rapid urease test (RUT) and non-invasive techniques such as serology, 13C-UBT, and detection of H.pylori antigens in stool samples. However, there is still no single noninvasive diagnostic test for the diagnosis of H.pylori in children, particularly in infants. The ideal test for diagnosis of H.pylori infection should be noninvasive, highly accurate, widely available and inexpensive. Furthermore, it should be able to discriminate the colonisation from H.pylori associated disease. In 2005, the Canadian Consensus group concluded that 13C-UBT is the best available and most reliable noninvasive test in children, but it is far less accurate in younger children (25). However, measuring urea hydrolysis rate (UHR) in addition to delta over baseline (DOB) values during 13C-UBT seems to be promising even in younger children (41,42).

In 1998, an enzyme-linked immunoassay in stools was approved by the FDA for both diagnosis of symptomatic patients and monitorisation of response to the treatment in adults. H.pylori faecal antigen (HpSA) examination is a highly reliable diagnostic method for H.pylori infection (1). It is used in epidemiological studies for determining the prevalence of H.pylori infections in asymptomatic subjects (5,19,21). Several studies about the accuracy of the HpSA test have related the use of faecal antigen in the diagnosis and follow-up of H. pylori infection (43). Today, monoclonal stool antigen tests are widely used and accurate for the diagnosis of H. pylori infection in children, but their use in young children is stil under investigation (44). In adults, the new biprobe real-time PCR assays applied to stool samples showed excellent results, Falsafi et al. (45) found a reasonable specificity of 92.3%, but a poor sensitivity of 62.5% in children. This study also noted an association between the density and severity of H. pylori gastrtis in histology and positivity of stool PCR. This could explain the lower sensitivity of the test in children who, for the most part, have milder degree of gastritis.

Serologic assays cannot be used on their own in children and adolescents for either diagnosis of H.pylori infection or to monitor the success of therapy because the sensitivity and specificity for detection of antibodies (IgG or IgA) against H. pylori in children varies widely (46). A positive IgG test can occur several months or even years after the infection thus cannot be used reliably for diagnosis or treatment outcomes.

Upper gastrointestinal system endoscopy with biopsies is the preferred method of investigation in children with upper digestive symptoms suggestive of organic disease and is the gold standard for diagnosing pathologies related to H.pylori. Recently, Guarner et al. published a ten-year review on diagnostic tests in children from 1999-2009, concluding that endoscopy with histopathology is the only method that can diagnose and confirm H.pylori infection, its associated lesions (atrophy, intestinal metaplasia) and other causes of symptoms as well (47). H.pylori infection usually causes diffuse antral gastritis and pan-gastritis in childhood (48,49). In H. pylori infection, endoscopic findings may be normal or there may be mild erythema or erosions in children. Gastric ulcer is a common finding in

childhood H.pylori infection, on the other hand, the presence of antral nodularity is a very common and higly suggestive endoscopic feature in children (49,50). The patchy nature of the infection and of gastric MALT lymphomas warrant the need to take multiple biopsies from gastric antrum, corpus and even cardia as an integral part of diagnostic endoscopy in children. Rapid urease test (RUT) can be performed in endoscopic biopsy specimens by using homemade or commercially available reagents. Since a significant association between density of H.pylori by histology and the possibility of a positive RUT has been demonstrated (51), the chance of detection of the bacteria may be increased by placing two biopsy specimens (one from antrum, one from corpus) into the RUT kit.

Fluorescent in situ hybridization (FISH) or PCR techniques can be applied to the frozen or parafin-embedded gastric tissues for the diagnosis of H.pylori infection. The major advantage of these methods is the ability to study antibiotic resistance in biopsy specimens. Culture is the only method that consistently has 100% specificity, but sensitivity varies depending on the experience of the laboratory (47). At present, culture procedures have not been standardised and relatively few clinical laboratories offer this service routinely in our country.

In summary, obtaining biopsies for tissue-based H.pylori tests requires performing an endoscopy which is an important component to defining the etiology of the patient's symptoms. Histopathology can assess the presence of H.pylori and infection associated lesions (i.e., intestinal metaplasia) and other unrelated pathologies. Of the tissue-based tests for H.pylori, rapid urease test has slightly better sensitivity and specificity than histopathology, culture is the only method with 100% specificity, but sensitivity varies depending on the experience of the laboratory, while PCR and FISH testing are still not widely used.

Treatment

In pediatric age patients RAP is not an indication for a "test and treat" strategy, but in recurrent abdominal pain (particulary epigastric pain) it is important to determine the cause of the presenting gastrointestinal symptoms. Hence, children with upper gastrointestinal symptoms should be investigated in order to understand the etiology of the symptoms and H.pylori infection should be included into the differential diagnosis. Guidelines on the management and treatment strategies for H. pylori infection were produced in the 2000 Maastricht Consensus Report and revised in Maastricht III report (Figure 2) (24). A register was established on the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) website to collect data on treatment performed by European paediatrician to inquire the treatment practices. Triple therapy for 2 weeks with amoxicillin 50 mg/kg divided twice a day and clarithromycin 15 mg/kg divided twice a day (or metronidazole or tinidazole 15 mg/kg divided twice a day) combined with omeprazole 1 mg/kg once a day is commonly used for the eradication of H.pylori in children and remains the suggested first-line eradication treatment (Table 2). The data collected from 23 centers (from 11 European countries) by the Pediatric European Register for Treatment of H.pylori (PERTH) revealed that the classical PPI-containing triple therapies used in adults do not seem to be as efficacious in children, and longer than 1 week treatment seemed to be solely more expensiive (52). The overall eradication rate was 65.6%, and it was significantly higher in children with ulcer (79.7%) compared to children without ulcer (63.9%, p = .001) (52). The H.pylori

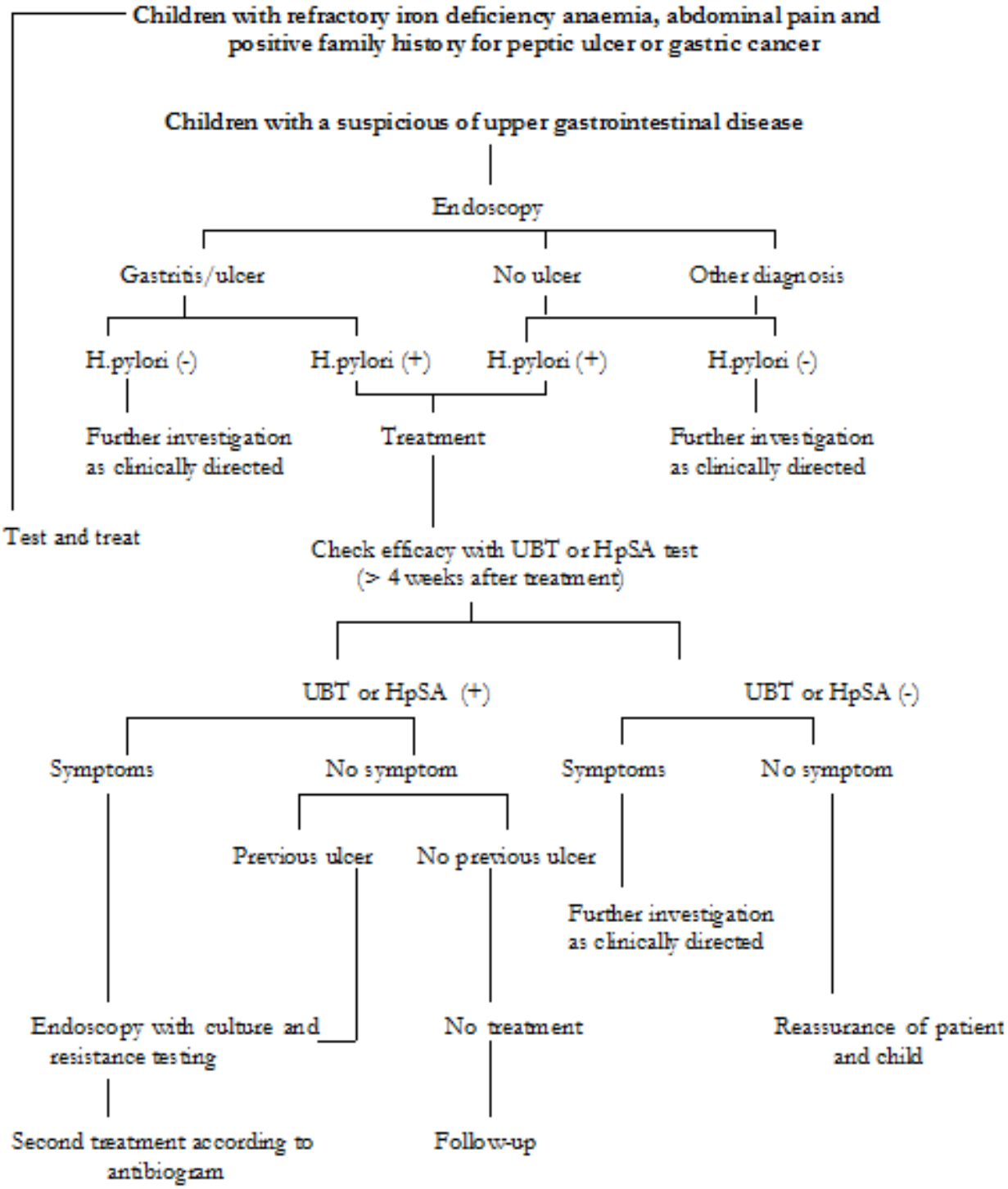

FIGURE 2 Algorithm for children having symptoms suspicious of *H. pylori* infection.

TABLE 2. Recommended eradication therapies for *H. pylori* disease in children: first-line options for two weeks.

DRUGS	DOSAGE	REGIME
Proton Pump Inhibitor		
Omeprazol	1 mg/kg	Once a day
Antibiotics		
Amoxicillin and Clarithromycin	50 mg/kg 15 mg/kg	Twice a day Twice a day
Amoxicillin and Metronidazole	50 mg/kg 15 mg/kg	Twice a day Twice a day
Clarithromycin and Metronidazole	15 mg/kg 15mg/kg	Twice a day Twice a day

eradication rate following standard triple therapies is largely decreasing all over the world and this phenomenon has been related to an increasing prevalence of bacterial resistance which varies between different geographical regions. The classical triple therapy for 14 days remains the first-line therapy in those areas where the primary clarithromycin resistance is lower than 15%. If this is the case, the combination of amoxicillin – metronidazole is preferrable if the metronidazole resistance is lower than 40% (24). The results of the PERTH demonstrated that bismuth-containing therapies as a first-line treatment were more efficacious than the classical PPI triple therapies, although less commonly used (52).

The sequential therapy is a simple dual (PPI plus amoxicillin) therapy of 5 days' duration followed by triple (PPI, clarithromycin and tinidazole/metronidazole) therapy of 5 days' duration. The sequential treatment, now widely used in adults, suggested superior eradication rates compard to conventional 7 or 10-day regimens (53,54). Francavilla et al. showed for the first time the superiority of a 10-day sequential treatment in children compared to the standard treatment, and an overall eradication rate of 85.2% was obtained in this study (53). The same group from Italy recently published the eradication rate of conventional clarithromycin based triple 7 day terapy and 10 day sequential treatment regimen on the clarithromycin resistant strains (55). It was found that sequential regimen has higher efficacy than standard therapy even in children with resistant mutation strains. However, the number of patients included in sequential trials and compliance concerns (changing medications at midpoint) remain to be solved by well designed multicenter studies in different geographical regions. Until then, classical triple therapy is the first-line eradication option for children.

Supplementation of Saccharomyces boulardi to H.pylori eradication regimens emerged as an alternative at the begining of 2000s (56). However, rather than being an additional therapeutic effect, probiotics significantly reduced the incidence of side effects (57). To date, the most reasonable policy to adopt is to treat a child according to the result of the antibiotic-susceptibility test whenever possible, or at least according to what is

known about the antibiotic susceptibility of H pylori strains cultured in this geographical area.

Antibiotic resistance

Drug resistance is a growing problem in adults as well as in children. Several H.pylori strains from Japanese children were studied in 2007 and high rates of primary resistance to clarithromycin (36.1%) and metronidazole (14.8%) were reported with consequences for the eradication rate (58). Double resistance was detected in 6.6% of the strains of Japanese children. A rather low clarithromycin resistance rate was reported from Asia (Malasia 2.1%, Taiwan 10.6%) and South America (Colombia 3.8%), in contrast to the high rates of metronidazole in those countries (59-61). A multicentric antibacterial resistance study which included children from 14 countries in Europe revealed a resistance rate of 25% to metronidazole, 24% to clarithromycin, and double resistance rate of 6.9% (62). In this study, resistance to amoxicillin was exceptional as expected. In Turkey, the susceptibility of 31 H.pylori strains to antibiotics was tested by using E-test method, and clarithromycin resistance was tested by FISH method. A very high resistance rates were found to clarithromycin, metronidazole and ciprofloxacin, 41.9%, 41.%, and 45.2% respectively (63). Resistance to amoxicillin and tetracycline was 3.2%.

Fluoroquinolone resistance is an emerging problem in adult population, and there is an increase in resistance to levofloxacin (64). However, fluoroquinolones have been less frequently used in children and adolescents and therefore the prevalence of resistance is lower. A study of 174 children in Israel revealed no resistant strains (65). Since the pattern of antibiotic resistance to H pylori has been changing in the course of time in different geographical ares, periodic monitoring of antibiotic susceptibility is mandatory to tailor treatment and prevent eradication failure.

Vaccination

Helicobacter pylori infection is usually acquired during childhood and tends to persist unless treated. It is highly prevalent all over the world and, an is an important cause of gastritis, peptic ulcer disease, gastic mucosa-associated lymphoid tissue lymphoma (MALT) and gastric adenocarcinoma. Treatment of H pylori requires multidrug regimens because of the barrier function of gastric mucus layer, and resistance is also an important issue with the antibiotics commonly used for eradication of the bacteria. Hence, a prophylactic vaccine, administered during infancy would obviate many treatment concerns and could be an attractive strategy to control H.pylori infection (66). Since the initial studies which demonstrated that it was possible to reduce gastric H.pylori colonization by vaccination with H. pylori antigen and adjuvant, various approaches including whole cell vaccines, recombinant antigens (e.g., urease A/B subunits, CagA, VacA, NapA, catalase, or heat shock proteins) in combination with bacterial toxins or other adjuvants have been successfully tested in animals, however similar vaccine trials in humans have shown adjuvant-related adverse effects and only moderate effectiveness (67-69).

It is obvious that infections caused by microorganisms that gain access to the body via the mucosal membranes are best prevented by mucosal vaccination. Further, vaccination at mucosal surfaces may stimulate both systemic and mucosal immunity; the latter not only at the site of vaccination, but also at distant mucosal epithelia (69,70). Transcutaneous immunisation may be

effective as a route for inducing protection against H. pylori colonization and warrants further studies.

Conclusion

Despite of decreasing prevalence of H. pylori worldwide, it is still one of a major health problems in developing countries. Optimal treatment of H. pylori infection in children depends on the sensitivity of the H.pylori strain to the given antibiotics. Unless wide spread use of antibiotic-susceptibility test is available, and as long as the treatment relies upon what it is known about antibiotic susceptibility of H. pylori strains the children are harboring in any particular area, antibiotic resistance issue will remain as an issue to be solved.

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