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Gastrointestinal Complaints and Treatment of *Helicobacter pylori* in Children: A Narrative Review

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Abstract

Context: The role of *Helicobacter pylori* infection in children's problems is considered in recent years. *Helicobacter pylori*, a gram negative spiral flagellate organism has diverse effects and consequences on children's health, but in some issues especially in chronic abdominal pain its role continues to debate. The prevalence of *H. pylori* infection and remedial measures against it in Iranian children is increasing.
Evidence Acquisition: Diagnostic tests are divided into two categories: Invasive and noninvasive. Diagnostic methods are available and although invasive methods are more accurate and reliable; non-invasive methods are more acceptable and practical for children. Serological diagnosis assays are not worth much in the pediatric fields.
Results: It is important to emphasize that diagnostic methods for *H. pylori* are revised and in some conditions, such as chronic abdominal pain, contrary to the impression, no treatment is required.
Conclusions: Triple therapy is a reasonable method to eradicate *H. pylori* in the first stage, but different combinations and one week courses in the Iranian studies were successful.

Keywords: Children, Epidemiology, Chronic Abdominal Pain, Treatment, *Helicobacter pylori*

1. Context

Helicobacter pylori (*H. pylori*) are acquired during childhood and lives long in the absence of treatment. Infection could be acquired at any age; however, the incidence is higher in children (1). *Helicobacter pylori*, in recent years are considered as an important cause of different diseases and problems in distinct fields of adult and pediatric health. Nowadays, there are many researches on the disease and symptoms attributed to interference of *H. pylori*. Although in some of the symptoms, such as short stature or immune thrombocytopenic purpura (ITP), this relationship seems a little irrelevant, there is convincing data in most of the articles and investigations in this issue are continuing.

Childhood is an important period for acquisition of *H. pylori* infection, which is usually acquired during the first years of life in both developing and industrialized countries (2). In the earlier texts, several gastrointestinal problems were attributed to *H. pylori*; therefore, eradication treatment was also carried out. However, the role of *H. pylori* in some gastrointestinal problems, especially chronic abdominal pain in children, is controversial and there are conflicting results. The current review aimed to explain epidemiology of this microorganism, focusing on Iranian children, and also the current opinion on diagnosis and the role of *H. pylori* in this issue and the first line treatment.

2. Evidence Acquisition

The following electronic databases were searched: Embase, Medline and web of science. The Cochrane library was also reviewed to find relevant articles. The search employed terms included "*Helicobacter pylori* or *H. pylori*", "Iran", "child or children", "diagnosis" and "therapeutics or treatment". Search strategies were made by different combinations of the search terms. The reference lists from primary and review articles were also searched. Language restrictions were considered for English and Persian. Authors excluded conference abstracts and letters to the journal editors because of their limited data. The qualitative results emanated from the reviewed articles were presented and discussed.

3. Results

3.1. Helicobacter pylori in Iranian Children

H. pylori infection is prevalent in Iran with the estimated prevalence of 65% (1). The epidemiology of *H. pylori* in pediatric and different regions of Iran is very diverse. In Shiraz, Alborzi et al. conducted a study on the stool antigen positivity of *H. pylori* and reported the prevalence of these bacteria as 98% in two-year-old children (3). Another study in the same city, Shiraz, by Dehghani et al. reported

that from 113 pediatric patients with abdominal pain and other dyspeptic symptoms 52% were positive for *H. pylori*, detected by the urea breath test (UBT) (4). In Rasht, about 40% of children aged 7 - 11 years were reported positive for *H. pylori* infection, through stool exam (5). A survey in Rafsanjan reported quite lower infection rate (52% in boys, 42% in girls); albeit in this study, serological methods were employed (6). A study by Rafeey and Nikvash on 96 children with dyspeptic symptoms in Tabriz showed that 35.4% and 64.6% of the subjects were positive for *H. pylori* antigen through stool exam and histology, respectively (7). Again in Tabriz, 806 adolescents aged 13 - 15 years were evaluated for the presence of *H. pylori* infection by stool antigen test which 35.2% were carrier (8). In another study by Maleknejad et al. 103 school children with abdominal pain were screened by serology and endoscopic evaluations. In serological test, 47 (45.6%) subjects were positive, while in pathological tests the infection rate was only 28.2% in the children (9). Two hundred seventy-eight children of 7 - 9 years old, selected by multistage random sampling in Zanjan were evaluated by serologic methods of anti-*H. pylori* antibody (IgG), which indicated the prevalence of 52.8% (10). The results of a recent study from Golestan province also suggested a high prevalence (52.5%) of *H. pylori* in children (11).

3.2. Chronic Abdominal Pain in Children and Role of Helicobacter pylori

Abdominal pain is a common complaint in childhood. Besides frequent reference of children with this symptom to general practitioners, internists, surgeons and psychologists, in fact pediatricians are the main point of this reference. The definition of chronic abdominal pain is used clinically and in research over the last 40 years has used the criterion of "at least three pain episodes over at least three months interfering with function" (12). In clinical practice, it is generally believed that pain that exceeds one or two months can be considered chronic. Surprisingly, etiology and approach to acute and chronic abdominal pain is different in many aspects and *H. pylori* are mainly evaluated in chronic abdominal pain and not in acute ones. Children and adolescents with chronic abdominal pain pose unique challenges to their caregivers and the physicians. Affected children and their families experience distress and anxiety that can interfere with their ability to perform regular daily activities (13). Abdominal complaints such as pain, nausea or other dyspeptic symptoms are nonspecific and can be caused by different organic diseases within and outside the digestive tract. The etiology is different intra-abdominal and non-gastrointestinal problems. Abdominal complaints may also be part of a functional gastrointestinal disorder (14). Functional abdominal pain is the most common cause of chronic abdominal pain. It is a specific diagnosis that needs to be distinguished from anatomic, infectious, inflammatory or metabolic causes of abdominal pain.

Helicobacter pylori are considered as the major cause of chronic gastritis and duodenal ulcer in childhood and an important cofactor in the development of gastric cancer (15). Whether *H. pylori* gastritis causes abdominal pain in the absence of peptic ulcer disease (PUD) is still debatable. Several studies showed improvement of symptoms after treatment; however, in some of the studies, success in eradication was not monitored and eradication of the bacteria was assumed in cases from symptomatic improvement (16).

In a large meta-analysis of more than 40 studies, the relationship between treatment of *H. pylori* and improvement of chronic abdominal pain was assessed and the results indicated that *H. pylori* infection was not associated with abdominal pain (17). Epidemiological studies on the prevalence of chronic or recurrent abdominal pain in children groups in various European countries showed that estimated frequencies ranging from 0.3% to 19%; but, the frequencies in different countries were not related to *H. pylori* prevalence in these countries (18). In fact more recent case-control studies confirmed the lack of evidence for a causal relationship between *H. pylori* infection and abdominal pain in children. In a study in Germany, Bode et al. identified that social and familial factors (single-parent household, family history of PUD, or functional pain) were significantly associated with abdominal pain, but not with the *H. pylori* status of the child (19). Tindberg et al. reported no significant association of recurrent abdominal pain with *H. pylori* infection in 695 schoolchildren of 10 - 12 years old. In fact, an inverse relationship was noted for *H. pylori* positivity and the occurrence of any abdominal pain after adjustment for the selected possible confounders (20).

There are other studies with a short follow-up period of only a few weeks. These uncontrolled intervention studies provided weak evidence of a causal relationship between *H. pylori* infection and abdominal pain; particularly, since functional abdominal pain resolves in 30% - 70% of patients by two to eight weeks after diagnosis accompanied by reassurance of the child and the parents (16).

Only one double-blind randomized placebo-controlled trial was performed on symptomatic children with *H. pylori* infection, excluding cases of PUD. Twenty children were studied for 12 months, and the relationship between symptom relief and controlling the bacteria or histological healing was not observed (21).

Therefore, based on this analysis and researches, at present, there is inadequate evidence supporting a causal relationship between *H. pylori* infection and abdominal symptoms in the absence of ulcer diseases.

3.3. Role of Helicobacter pylori in Other Gastrointestinal Symptoms of Children

There are various researches in Iran on the relationship between gastrointestinal problems and *H. pylori* infec-

tion. In a study by Shokrzade et al. they evaluated pediatric patients with dyspepsia for *H. pylori* by endoscopy. Among the 303 patients, 263 (86.8%) were found to be positive for *H. pylori* antigen and among 250 patients with abdominal pain, 219 (87.6%) were infected with these bacteria. An unexpected observation in this study was that the infection rate was higher in the symptomatic patients of younger age. The treatment and its effects on symptoms were not evaluated (22).

The interaction between *H. pylori* infection and gastroesophageal reflux disease (GERD) is widely debated in the literature over the past decade, and the impression that treatment of these bacteria can increase GERD was the subject of many publications with contradictory conclusions in children and in adults (22). Certain studies showed that *H. pylori* inversely correlated with the prevalence of GERD and aggravation of esophagitis after eradication (23).

An important issue of concern in *H. pylori* infection is gastrointestinal and especially gastric malignancy. In 1994, the world health organization (WHO) declared *H. pylori* as a class I carcinogen. The risk of gastric cancer not only depends on the infection itself but also is strongly modified by the presence of bacterial virulence factors (16). Other factors such as the genetic background of the host and environmental influences, including diet, also have various influences (24). The eradication of *H. pylori* may have the potential to decrease the risk of gastric cancer. Individuals with a positive family history for gastric cancer are considered a high-risk group. There is strong agreement that in children with a first-degree relative with gastric cancer, test for *H. pylori* infection should be considered (16).

3.4. Role of Helicobacter pylori in Non-Gastrointestinal Symptoms of Children

Iron-deficiency anemia in children and adolescents may have different causes. Based on many publications, if noninvasive diagnostic tests are unable to find the cause and/or if the iron deficiency is refractory to oral iron therapy, then diagnostic upper endoscopy is required. This can reveal bleeding, mucosal involvement and infection. Several studies showed an association between low iron status and *H. pylori* infection (16). Since both *H. pylori* infection and iron deficiency are associated with poor socioeconomic and hygienic conditions, cross-sectional studies cannot determine the cause and effect of variables (16).

A wide variety of extra intestinal manifestations are suggested to be associated with *H. pylori* infection; for example: Otitis media, upper respiratory tract infections, periodontal disease, food allergy, sudden infant death syndrome (SIDS), idiopathic thrombocytopenic purpura and short stature; however, the current evidence for a causal relation for these associations in children is not compelling.

3.5. Definite Diagnosis of Helicobacter pylori in Children and Misconceptions

Unfortunately, in approaches to diagnose *H. pylori*, mistakes occur due to inadequate knowledge of exact and mode of diagnostic plan. Children differ from adults with respect to *H. pylori* infection based on the prevalence of the infection, the complication rate, the detection of gastric malignancies, age-specific problems with diagnostic tests and drugs and a higher rate of antibiotic resistance (16).

Several invasive and noninvasive diagnostic tests are used to detect *H. pylori* infection, but the value of these tests in children is quite different. Significant errors in carrying out these tests in children may occur which originate from application of adults study to pediatrics. This process leads to over diagnosis and unnecessary treatment in children.

Firstly, it should be mentioned that serological tests are not useful to diagnose active *H. pylori* infection or monitor eradication therapy (25). In fact, histological examination is the most accurate method to diagnose *H. pylori* infection in children, although this procedure is invasive and not pleasant and acceptable by children and their families (26). Upper gastrointestinal endoscopy with biopsies is recommended as the initial test to evaluate peptic or reflux related symptoms that may be associated with *H. pylori*. However, patients who refuse endoscopy or patients who require follow-up to treat can be evaluated by a non-invasive test (26).

The 13C-urea breath test (UBT) is a non-invasive and accurate means to document *H. pylori* infection. UBT can be used in children to diagnose *H. pylori* infection and confirm eradication as a valuable plan with high sensitivity (27). In older children, UBT is 100% sensitive and 92% specific to diagnose these bacteria when compared to culture or both histological tests and RUT (28). However, the test specificity decreases in young children because UBT requires active cooperation of the child in swallowing the capsule and insufflations of the instrument and there is need to specialized laboratory equipment.

Detecting bacterial antigens in stool (HpSA; *H. pylori* stool antigen) is an alternative noninvasive practical diagnostic test. Its performance in children and teenagers is tested in some developed countries; in Iran, Iranikhah et al. showed for this test, a sensitivity and specificity above 90%; however, its accuracy in the developing countries is not well established (29). They detected *H. pylori* antigen in stool using either polyclonal or monoclonal antibodies. Some use polyclonal antibodies which are highly sensitive and specific for the diagnosis of this infection in adults and children. A few studies on children found comparable efficacy between UBT and HpSA (25). Limitations of the HpSA include inter-test and lot-to-lot variability, cutoff values and lower accuracy after eradication therapy. Few studies using a novel monoclonal immunoassay for *H. pylori* stool antigen (FemtoLab) were recently published in both children and adults (25).

Serologic test; mostly used but wasteful in diagnosis: *Helicobacter pylori* infection induces an early increase of specific IgM and a later and persistent increase of specific IgA and IgG antibodies. These antibodies can be detected in whole blood, serum, urine, and saliva (30). In general, serologic tests cannot be used on their own to diagnose *H. pylori* or to monitor eradication since their sensitivity and specificity to detect antibodies (IgG or IgA) in children are low and vary widely. Specific IgG may remain positive for several months or even years after resolving the infection. Thus, the tests cannot be used reliably for treatment success. Many tests based on the detection of antibodies are commercially available, easy to perform and inexpensive. In spite of these advantages, they are not recommended for clinical practice in pediatric patients by the later American, Canadian or European consensus statements (16). IgA-based tests can only detect 20% - 50% of *H. pylori*-infected children, and are not suitable for diagnosis. The use of cutoff value limits obtained in adult studies results in a failure to detect a large proportion of infected children, especially in children younger than six to eight years. Tests based on the detection of antibodies (IgG, IgA) against *H. pylori* in serum, whole blood, urine, and saliva are not reliable in the clinical settings. Iranikhah et al. in their study in Iran demonstrated that low-cost and rapid diagnostic technique, stool antigen test, was highly sensitive and specific to detect *H. pylori* infection in children with recurrent abdominal pain (29).

3.6. Treatment of Helicobacter pylori in Children

Although it seems that the effective treatments in adults will also be effective in children, the most efficient treatment for *H. pylori* eradication in children needs to be determined. Drug resistance and side effects, intolerance due to long time therapy are amongst the causes of treatment failure.

Triple therapy is the most frequently used regimen in children, but different eradication rates in different areas were reported because of different host factors, characteristics of the microbial strains and antimicrobial resistance acquired during the treatment. The goal of treatment is at least a 90% eradication rate at the first attempt (15). A high initial eradication rate will prevent the development of antibiotic resistance and spread of resistant *H. pylori* strains in the population. A high initial success rate will reduce the need for further treatments and procedures, including endoscopies.

The combination of two antibiotics and a proton pump inhibitors (PPI) is the recommended first-line therapy since the first published pediatric guidelines (Box 1) (31).

First-line eradication regimens based on evidence-based "guidelines from European society for pediatric gastroenterology, hepatology and nutrition (ESPGHAN) and a north American society for pediatric gastroenterology, hepatology, and nutrition (NASPGHAN) for *Helicobacter pylori* infection in children" are as follows: 1) triple therapy with a PPI plus amoxicillin and metronidazole; or 2) triple therapy with a PPI plus amoxicillin and clarithromycin; or 3) bismuth salts plus amoxicillin and metronidazole; or 4) sequential therapy (Box 1). Clarithromycin-based triple therapy can only be recommended as the first-line therapy if susceptibility testing in the individual patient reveals a clarithromycin-susceptible strain or the clarithromycin resistance rate in this area is known.

Double resistant *H. pylori* strain recommendation is as follows: High-dose amoxicillin, metronidazole, and esomeprazole for two weeks (16).

In Iran, resistance to metronidazole and sensitivity to clarithromycin were reported in some studies. Mirzaei et al. indicated 37.5% *H. pylori* resistance to metronidazole in 15 to 58 year old Iranian patients (32).

Najafi and Seighali in a survey treated patients by a seven-day triple therapy using omeprazole, clarithromycin and metronidazole and this protocol was greatly efficient (84.2 %) to control *H. pylori* in children (1).

New investigations provided evidence suggesting that probiotics modulate *H. pylori* colonization of the gastric epithelial cells. Many studies documented the effectiveness of prophylactic probiotics in association with antibiotics to modify *H. pylori* eradication rate and the antibiotic associated gastrointestinal side-effects during eradication therapy. Khodadad et al. evaluated adding probiotics to treatment regimen in Iranian children.

Their study showed that probiotics had positive effect on the eradication of *H. pylori* infection and they recommended adjuvant therapy with probiotics in order to reduce the frequency of antibiotic induced side effects during treatment with antibiotics (33).

Box 1. First-Line Treatment Recommendations to Control *Helicobacter pylori* in Children

Recommendations[a]
PPI (1 - 2 mg/kg/day) + amoxicillin (50 mg/kg/day) + metronidazole (20 mg/kg/day) (twice daily for 10 to 14 days)
PPI (1 - 2 mg/kg/day) + amoxicillin (50 mg/kg/day) + clarithromycin (20 mg/kg/day) (twice daily for 10 to 14 days)
Bismuth salts (bismuth subsalicylate or subcitrate 8 mg/kg/day) + amoxicillin (50 mg/kg/day) + metronidazole (20 mg/kg/day) (twice daily for 10 to 14 days)
Sequential therapy; PPI (1 - 2 mg/kg/day) + amoxicillin (50 mg/kg/day) (for five days); then PPI (1 - 2 mg/kg/day) + clarithromycin (20 mg/kg/day) + metronidazole (20 mg/kg/day) (for five days)

Abbreviation: PPI, proton pump inhibitor.
[a]Maximum daily dose for amoxicillin: 2000 mg, for metronidazole: 1000 mg, for clarithromycin: 1000 mg/day.

The reinfection rate reported in pediatric studies varies from 2% to 12.8% per patient year (34).

Iran is among the countries with high prevalence rate. Najafi et al. had studied the reinfection rate, which was 14.7% per patient per year (35).

4. Conclusions

The prevalence of *H. pylori* in the Iranian children is considerable and studies in this field on pediatric is unavoidable. Disease and problems caused by *H. pylori*, indication and methods of treatment in children are different from those of adults.

Although chronic abdominal pain is a common symptom in pediatric group, routine diagnostic challenges and eradication of *H. pylori* are not recommended in primary investigations. Large meta-analysis and multiple studies showed that eradication of *H. pylori* does not treat chronic abdominal pain significantly. Serologic tests are not proper modes of *H. pylori* diagnosis and the stool antigen can be used as a simple noninvasive practical route of diagnosis. The best first line therapy for these bacteria is a combination of proton pomp inhibitor plus amoxicillin plus "clarithromycin or metronidazole". Clearly, studies on antibiotic sensitivity and resistance of *H. pylori* in children are scarce and are highly suggested as research issues.

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