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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Prevention of *Helicobacter pylori* infection in childhood

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Abstract

Helicobacter pylori (*H. pylori*) infection is one of the most common infections worldwide. Although infection rates are falling in the developed and developing countries, *H. pylori* is still widespread in the world. This article has reviewed the important publications on *H. pylori* in childhood with a focus on its evolving transmission route and the source of infection and preventive strategies in childhood, PubMed was searched up to identify eligible studies. Relevant publications were searched using the following.

Key words: Children; Growth retardation; *Helicobacter pylori*; Iron deficiency; Prevalence; Prevention; Transmission

Core tip: This review has focused on transmission route and the source of *Helicobacter pylori* (*H. pylori*) infection and preventive strategies in childhood. The best way to decrease the prevalence of *H. pylori* infection in children is to educate women about how to protect themselves and their offspring from *H. pylori* infection. *H. pylori* infection rates may be decreased dramatically with improvements in sanitary infrastructure and household hygienic practices.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is common all over the world. The prevalence of *H. pylori* differs significantly both between and within countries. The high risk of intrafamilial infection was shown in the previous studies[1-7]. It is believed that in the vast majority of infected individuals, infection is acquired during early childhood[6-9]. The mother probably plays a key role in transmission[2-5]. In order to design preventive strategies, the elucidation of the mode of spread of this pathogen is very important. Primary reservoir is the stomach, and the bacteria are most likely spread from person to person through fecal-oral or oral-oral routes. Infection is often associated with poor sanitation, crowded living conditions, and poor water supplies[10].

PREVALENCE

The incidence and prevalence rates of *H. pylori* infection in childhood can vary greatly by nation and regions in same country. Fortunately, the prevalence rates in the world are getting decrease even in children. Estimated prevalence is almost 70% in developing countries and 30%-40% in the United States and other industrialized countries[11]. While there is a decline in the prevalence of *H. pylori* infection in northern and western European countries, the infection is still common in southern and eastern parts of Europe and Asia[9].

Prevalence of H. pylori infection in children

It is believed that *H. pylori* is mainly acquired during childhood[12,13], once established, may persist through-

out life[14]. Little is known about its age of onset, rate, or mode of colonization. The proportion of infected children increases with age. By the age of 10 years most children in developing countries have been infected by *H. pylori*[15,16]. Vanderpas *et al*[17] found that the prevalence of *H. pylori* was 18.2% in children aged < 6 years and 49.3% in adolescents aged 12-17 years. In the study of Zhang[18], the *H. pylori* infection rates in 3 to 7-year old, 8 to 12-year old and 13 to 16-year-old children were 39.5%, 41.0% and 54.5%, respectively. Rothenbacher *et al*[8] also found 8.9% in the 1-year-old children, 36.4% in the 2-year-old children, and 31.9% in the 4-year-old children. In the 603 subjects of *H. pylori* negative, 38.7% became infected within 12 years. Ertem *et al*[19] found that the prevalence was 18.2% under 4 years, 41% at 4-6 years, 48.6% at 6-8 years, 50% at 8-10 years, and 63% at 11-12 years of age. A prospective longitudinal cohort study (aged between 3 mo and 2 years) followed at 3-mo intervals for 2 years. The prevalence rose from 19% at 3 mo of age to 84% by 30 mo of age[6].

The prevalence of *H. pylori* differs significantly both between and within countries. The prevalence by age has decreased along with socioeconomic development. In a study including 22 centers from Czech Republic (aged 5-98 years), an significant decrease in prevalence from 2001 (41.7%) to 2011 (23.5%) was noted. It has been explained by improving socio-economic conditions and standards of living together and falling fertility rates[20]. Decrease in the prevalence in children was also reported in Estonia (in children from 42% in 1991 to 28% in 2002)[21] and Russia (in children from 44% in 1995 to 13% in 2005)[22]. The decline in the prevalence of *H. pylori* has been explained by the socio-economic changes after the fall of communist regimes[23]. Seroprevalence also varied significantly with the educational level, the water supply and the number of persons per room[4].

However, several studies recently showed that the prevalence of *H. pylori* is also declining among children in developing countries despite poor standard of living and low socio-economic conditions[20,24-26]. In a study from Turkey, the overall prevalence of *H. pylori* in children (aged 7-14 years) was 78.5% in 1990 and 66.3% in 2000[27]. In 2008, it was 30.9% between 2 and 12 years of age[2]. In the geographically large countries, prevalence rates have changed between regions and ethnic groups because of changing facilities and traditions. While the prevalence was 7.1% in a study from Canada, this rate was found as 42% among ethnic minorities[28].

CONSEQUENCES IN *H.PYLORI* INFECTION

Gastric ulcer and cancer

H. pylori is recognised as a cause of gastritis and peptic ulcer and it has been classified as a group A carcinogen by World Health Organization (WHO). Infected persons have a 2- to 6-fold increased risk of developing gastric cancer and mucosal associated-lymphoid-type (MALT) lymphoma compared with their uninfected counterparts. Recent studies have shown an association between long-term infection with *H. pylori* and the development of gastric cancer. Gastric cancer is the second most common cancer worldwide. However, it is unclear whether *H. pylori* eradication will improve outcomes in patients with gastric cancer[29].

Bronchial asthma

Recently, it was pointed out that the higher hygiene standards modulates the development of the immune system (Th1/Th2 shift of $CD4^+$ T-lymphocytes) and thereby increases the risk of bronchial asthma[20]. An increased prevalence of allergic diseases could be explained by the decreased incidence of *H. pylori* infection. Some evidences indicate an inverse association between *H. pylori* and asthma, but some studies did not support this data. In a meta-analysis of eight studies involving 14972 participants by Wang *et al*[30], it was found a weak evidence for an inverse association between asthma and *H. pylori* infection both in children and in adults. A group from Switzerland showed us the possible mechanisms of preventing allergic airway disease by *H. pylori* infection. They demonstrated that *H. pylori* inhibited the maturation of dentritic cells and therefore failed to induce T-cell effectors functions in mice[31]. In contrast to these results, a large Dutch study did not confirm any association between *H. pylori* seropositivity and wheezing, allergic rhinitis, atopic dermatitis or physician-diagnosed asthma[32]. Therefore, based on currently available data, no conclusion on the association between *H. pylori* infection and reduced risk of allergies can be established.

Growth retardation

There are conflicting reports regarding the association of *H. pylori* infection with growth failure. In the study of Dehghani *et al*[33] from Iran, there was no meaningful relationship between standard deviation score (SDS) (for height and BMI) and *H. pylori* infection. In Soylu *et al*[34] study, anthropometric variables were similar in the *H. pylori* [+] and [-] groups. However, according to Süoglu *et al*[35], mean ± SD height and weight for *H. pylori* positive were lower than those of the *H. pylori* negative. A few studies showed that ghrelin level decrease in children with infected *H. pylori* and eradication of infection correct the growth parameters[36-38]. Ozen *et al*[36] pointed out that among biochemical parameters, only ghrelin levels were associated with *H. pylori* infection.

Iron deficiency

Harris *et al*[39] suggested that hypochlorhydria in *H. pylori* infected children may be the role in the aetiology of iron deficiency. A study from Latin America determined that the serum ferritin and haemoglobin concentrations were low in *H. pylori* infected children[40]. The mean serum Fe and ferritin levels of *H. pylori* negative group were significantly higher than those of *H. pylori* positive ones[35]. These results show us the effects of *H. pylori* on multiple

factors and low socioeconomic conditions facilitate it.

TRANSMISSION

The primary modes of transmission are thought to be fecal-oral and oral-oral, but some indirect evidence has also been published for transmission *via* drinking water and other environmental sources[41]. The patterns of spreading of *H. pylori* under conditions of high prevalence differ from those in developed countries.

Transmission may occur in a vertical mode (*e.g.*, from parents to child) or in a horizontal mode (across individuals or from environmental contamination). Studies supports both intrafamilial and extrafamilial transmission[41]. Some previous studies[1-6] indicated that having infected family members is highly associated with the infection in children. Konno *et al*[1] identified fingerprint patterns identical to those of at least one family member in 76% of the children, with a significantly higher rate of identity in the mothers' patterns, compared with those of fathers. Mother-to-child transmission was thus suggested as the most probable route of transmission of *H. pylori*. Several studies pointed out that seroprevalence was higher in children whose mother was infected[2-4]. The relation between index child infection and the proportion of seropositive family members may reflect an increased probability of *H. pylori* exposure in families[3]. In a study, *H. pylori* was detected in 70.6% of children whose mothers were positive[2]. Within the Ulm Birth Cohort Study, which consisted of 1066 healthy newborns followed up to age 4, and their siblings and parents. In multivariate analyses, only maternal infection determined as the single risk factor (OR = 13.0) for acquisition of infection in childhood[5]. The mothers taking care of children probably play a key role in transmission[2-5].

Some studies have addressed the potential role of various family members simultaneously[6,7]. Kıvı *et al*[3] pointed out the presence of infected siblings as an independent risk factor for the infection in children. In addition, a Japanese study highlighted the role of grandmothers in the familial transmission of *H. pylori*. The siblings carried the main risk, followed by mothers and grandmothers but not by fathers and grandfathers[7]. The role of grandmothers who taking care of their grandchildren was an interesting determination. The importance of infected mothers and the lack of a significant contribution from infected fathers possibly reflect how intimate contact potentiates the effect of having seropositive family members. Person-to-person transmission and intrafamilial spread seem to be the main routes, based on the intrafamilial clustering observed, while a waterborne infection remains possible.

In high-prevalence areas, opportunities for horizontal transmission are higher, which can result in greater diversity of *H. pylori* within a family. Horizontal transmission occurs frequently between persons who do not belong to a core family in developed countries. Intra-familial transmission of *H. pylori* was common in urban families. However, the South African families were infected with widely diverse strains, and multiple infections were common.

Gastroenteritis, particularly with vomiting in an *H. pylori*-infected person can be a source of *H. pylori* in humans[42]. Exposure to an infected household member with gastroenteritis have associated with a 4.8-fold increased risk of infection among 2752 household members. Vomiting was associated with a 6-fold greater risk for new infection[43,44]. As with other enteric infections, *H. pylori* infection rates have decreased dramatically with improvements in sanitary infrastructure and household hygienic practices.

Moreno and Ferrus[45] were able to culture *H. pylori* from 6 of 45 wastewater samples. Another study claimed the isolation of *H. pylori* from five water samples originally from a river in Isfahan, Iran[46]. In the Karachi, Pakistan, 2 of 50 drinking water samples tested were found to be positive for *H. pylori* by PCR[45,47].

Day-care centers and H. pylori infection

The possibility of *H. pylori* transmission among children in day-care centers or kindergarten where interpersonal contacts are common have been also suggested. However, a meta-analysis of 16 studies did not confirm this hypothesis[48]. According to a study comparing three socioeconomic settings, children spending the whole day at home with their mothers were more susceptible to infection by *H. pylori*[2]. The mother is likely to have introduced the infection to her offspring. Child-to-child transmission outside the family has low possibility according to a study from Sweden[3]. Mother's *H. pylori* infection and close contact with her child all day are the main causes of contamination of children[2].

Contribution of living conditions of the family

The rate of *H. pylori* infection in high-income families was lower than that in middle to low-income families (36.9% *vs* 48.3%). In addition, the rate of *H. pylori* infection in children with well-educated parents was found lower than in those with parents who had not received higher education (39.5% *vs* 50.8%)[18].

The prevalence (34%) of *H. pylori* was significantly higher in lower economic status groups, in children living in crowded houses, and in older age groups[36]. There was a strong inverse correlation between family income and seropositivity[4]. Among study subjects aged 15+ years, prevalence of *H. pylori* infection was significantly increased in those with lowest education (OR = 3.19)[20]. In a study which comparing with three socioeconomic settings, the prevalence rate was the highest in children whose mother had lowest educated levels. The children who had illiterate mothers also had an increased prevalence of *H. pylori* infection. On the other hand, illiterate mothers was living in the deprivation area also[2]. Furthermore, the mother may be more important infection source than siblings in high-income countries and vice versa in low-income countries[49,50].

The prevalence of *H. pylori* (79.4%) in adults differed

significantly among the six Latin American countries studied. *H. pylori* positivity increased with increasing number of siblings. Odds of *H. pylori* infection increased with the presence of certain living conditions during childhood including having lived in a household with lack of indoor plumbing and crowding[51]. The incidence of *H. pylori* positivity increase with family size[2,3]. The lowest ratio of *H. pylori* was in mothers with one child[2].

Breastfeeding

Several studies have investigated the association between *H. pylori* and breastfeeding with conflicting results. The most of the studies supported the preventive effect of breastfeeding[19,52]. However, some studies were not able to confirm these findings[3,53,54]. In a cross-sectional study of 327 Turkish preschool children, Ertem *et al*[19] reported an OR of 0.22 and Rothenbacher *et al*[55] reported an OR of 2.57 in 946 German preschool children for *H. pylori* infection among children who were breast-fed[52].

In a systematic review by Chak *et al*[52] have not also determined the dose-dependent protective effect against *H. pylori* associated with increasing duration of breastfeeding. In a previous study[2], the highest HpSA positivity was reported in children who had been breastfeeding for 12 mo (33.3%). The prevalence of *H. pylori* was 5.8% in children who had never been breastfed. In a population-based study, it was 8.4%[55]. Several studies claimed that prevalence was the highest in children breastfed more than 6 mo[56,57]. In the study of Sýkora *et al*[58], the prevalence was 7.1% among 1545 children (aged 0-15 years). *H. pylori* was found in 12.4% of children that were not breast-fed. However, the prevalence of *H. pylori* was 80.8% among subjects living in children's homes in this study.

Appelmelk *et al*[59] reported that lactoferrin from human breast milk was able to bind to *H. pylori* liposaccharide, leading to its inactivation. Thomas *et al*[60] also determined that increased titers of *H. pylori* IgA in breastfeeding of the Gambian mothers can delay acquisition of infection in their children[60,61]. According to these data, the mothers in developing countries could have higher titers of *H. pylori* IgA in their breast milk.

STRATEGIES FOR THE PREVENTION OF *H. PYLORI* INFECTION IN CHILDHOOD

H. pylori infection is recognised as a cause of gastritis and peptic ulcer disease. The important question which needed research is the acquisiting time of *H. pylori* in childhood. Acquisition seems to occur mainly between the first and the second years of life. Therefore preventive measures need to be applied early childhood.

The high prevalence in parents and the child infection may originate in worse living conditions, poorer sanitation or more frequent gastroenteritis. More contacts with infected individuals in the extended family or community could also contribute to the higher risk of contacting the infection in low-income countries[3]. In early childhood, the mother is the family member with the closest contact with the child. It seems possible that mouth secretions of the mother which contaminated with *H. pylori* may transmit to the infant[62]. Transmission may also occur by the common use of spoons, the licking of pacifiers, the teats of feeding bottles or even by chewing or tasting children's food. Gastric juice, saliva and faeces have been postulated as vehicles for *H. pylori*[3,50]. For these reasons, not using the same tooth-brush or glass, not putting the materials which belong to babies into the mouth and washing hands are critical to prevent contamination of *H. pylori* infection. Herrera *et al*[63] compared *H. pylori* genotypes from members of low income families in Peru. Interestingly, in 70% of the cases, family members-child strain pairs did not match. The important effect of this study is to show the contribution of the living conditions to the spread of infection in traditional close relations of whole people in villages. In contrast to living as a core family, sharing the same living space in villages is prominent in most of the low income countries.

In poor resource settings where malnutrition exist, parasitic/enteropathogen and *H. pylori* infection co-exist in young children[64]. Like many common gastrointestinal infections, poor standard of living, low socio-economic status, overcrowded families and low education of parents are still major risk factors of *H. pylori* infection. Acute infection with *H. pylori* can lead to hypochlorhydria, which could facilitate the colonization of enteric infectious agents and subsequently may predispose to diarrhea and malnutrition[62]. Malnutrition that is caused by poor hygiene, recurrent infections and consumption of insufficient food increases gastrointestinal infections and also *H. pylori* infections. Poor living conditions, lack of facilities, low incomes, high numbers of children can cause serious problems in both feeding and maintenance aspects. However, the relationship between growth retardation and *H. pylori* is significant in the studies[33-36].

The prevalence of *H. pylori* infection has been decreasing in the white race among immigrants. However, the people with African and Asian origin have the same results like developing countries[10]. It confirms with the effects of keeping traditional life or the higher *H. pylori* prevalence rates in their countries of origin. In addition, the comparison of educational levels of these people is also important. Even in improving living conditions, no serious decrease in the rate of infection shows us the importance of hygiene habits of the family. This study indicates that main causes are not the lacking of in-home facilities but the education and consciousness.

Epidemiologic studies regarding the role of breastfeeding in protecting against *H. pylori* infection have produced conflicting results. At least, the question is not whether breastfeeding protect the baby against *H. pylori* infection. The real problem is the breastfeeding methods being done with suitable sanitary rules. Not washing hand before breastfeeding may be the main reason for passing the infection to their baby. It has been emphasized that horizontal contagion of infection from nipple to child

might occur in unhygienic mothers[57]. The close maternal contact may be a possible route of transmission of *H. pylori* infection. Hypothetically, the more the duration of breastfeeding lasts, the greater the baby exposes unhygienic conditions and becomes infected by *H. pylori*.

There was an interesting determination from Gambia. The children living in the same family compound, with the same father but different mothers, were colonized from 3 mo of age while their half-siblings remained free from colonization to age 1 year. It was claimed that the colonized mothers have different levels of anti-*H. pylori* IgA in breast milk and high levels of which are associated with delayed infant *H. pylori* colonization[6].

Probiotics improve gastrointestinal flora and prevent to settle the infective agents. Probiotics have contributed in supportive therapy in *H. pylori*[3]. The antibiotic treatment has a high cost and is not 100% effective because of resistance to antibiotics. Probably, using probiotics as a prophylactic functional food for preventing infections in children and their mothers in daily life could be effective. However, in low income societies in which the *H. pylori* prevalence rate is higher, this can be a utopia because of cost-efficiency problems.

In the contagious diseases, everybody can be infected when there is an index case in the home. Moreover, *H. pylori* has high risk for reinfection. There can be two reasons: (1) The hygiene habits and the difficulties to reach clean water resources have not been improved; and (2) The transmission of infection among the people living in the same home has repeated. In this situation, the eradication of infection cannot be possible without dried sources. Like the eradication of parasitosis, parasitosis is also a disease of bad sanitation, and the screening of whole family and the proper therapy of infected cases can be necessary for accurate eradication of *H. pylori* infection and probably, the chain of infection can be broken. However, it can not be cost-effective. Also, therapy in children is not recommended except limited indications. Nowadays the most suitable approaches in order to decrease the risk of gastric cancer in the future can be scanning the older people having index cases and the children having gastrointestinal symptoms, and treating infected cases in home. The prevalence of *H. pylori* infection in childhood is decreasing, especially in developed countries. Among the risk factors explored, low socioeconomic status, limited education, crowded homes and difficult access to sanitized water are the most significant factors affecting the prevalence of *H. pylori*.

In future, vaccinia may be a chance to prevent infection. According to the initial studies, the decrease gastric *H. pylori* colonisation by vaccination with *H. pylori* antigen and adjuvant was possible[65,66].

CONCLUSION

In conclusion, whole these studies support that *H. pylori*-infected mothers and siblings are primary determinants for childhood *H. pylori* infection being consistent with a predominantly mother-child and sib-sib transmission. Intimate contact has been suggested to be important. Most of the studies have indicated mothers or persons who looking after the children. Training the parents, especially mothers and grandmothers, about sanitation rules besides reaching safe water supplies, participating in "screen/therapy/follow up for recurrence" programme in adults who have gastrointestinal problems should be crucial. Washing hands thoroughly, eating food that is properly prepared and drinking water from a safe, clean source are important steps for preventing *H. pylori* infection in children. Breastfeeding makes the children healthy, but hand washing practice before breastfeeding and preparing food will be easy and more effective to prevent household contamination. *H. pylori* infection rates may be decreased dramatically with improvements in sanitary infrastructure and household hygienic practices. The best way to decrease the prevalence of *H. pylori* infection in children is to educate women about how to protect themselves and their offspring from *H. pylori* infection.

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