

***Helicobacter pylori* in Children: An Indian Perspective**

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Helicobacter pylori is causally associated with peptic ulcer disease and gastric carcinoma. Typically children get infected with this organism during the first decade of life but diseases, associated with *H. pylori*, are seen mainly in adults. In India, almost 80% of population is infected with *H. pylori* and most of them by 10 years of age. Hence, it is important for a pediatrician to know when to suspect this infection, how to investigate and how to treat it. Extensive electronic (PubMed) literature search was done for this review and literature (randomized controlled trials, clinical trials, meta-analysis, practice guidelines) related to *H. pylori* in children were reviewed. Special emphasis was given to Indian studies. From this review we can conclude that *H. pylori* infection is very common in Indian children especially in the low socioeconomic status but most infected children remain asymptomatic through out their childhood and about 15% develop peptic ulcer disease as young adults and 1% develop gastric cancer in older age. There is no association, what so ever, of *H. pylori* infection and recurrent abdominal pain (RAP). Endoscopy is the preferred method of investigation in children with upper digestive symptoms suggestive of organic disease. Children with *H. pylori* related disease (peptic ulcer, primary gastric B-cell lymphoma and atrophic gastritis with intestinal metaplasia) but not mere *H. pylori* infection should be treated with the triple drug regimen comprising of proton pump inhibitor (PPI) and two antibiotics for two weeks.

Key words: *Helicobacter pylori*, Recurrent abdominal pain.

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Introduction

The Medicine Nobel Prize of 2005 was awarded to an observant pathologist Robin Warren and an enterprising physician Barry Marshal, both from Australia, for the discovery of *Helicobacter pylori* (*H. pylori*) and its role in peptic ulcer disease and gastritis in 1983(1). This organism has fulfilled Koch's postulations as a cause of chronic active gastritis in human(2). Since its discovery, the organism has generated tremendous interest among the medical fraternity. On MEDLINE search, till January 2007, there are 23,256 publications (2,103 of them are in children) and a full journal (*Helicobacter*) has been devoted to this organism. However pediatric literature related to *H. pylori* from India is relatively scanty(3-9).

Helicobacter pylori is a slowly growing, microaerophilic, highly motile, gram-negative spiral organism with 4-6 flagella at one end. The organism has the striking biochemical characteristic of abundant urease enzyme production. This enzyme is important for colonization and is an indirect marker of the organism's presence, as it is the basis of rapid urease test (RUT), the urea breath test and as an antigen for a serological test. *H. pylori* has a special affinity for gastric mucosa and is etiologically associated with chronic active gastritis, peptic ulcer (duodenal and gastric) and gastric cancer. However, the relationship between this organism and gastro-duodenal complaints in children is not clear. Chronic gastritis induced by *H. pylori* is usually not symptomatic but is considered to be the background of several diseases, *i.e.*, peptic ulcer disease and gastric malignancies that typically occur in adulthood. *H. pylori* infection is almost always acquired in early childhood and usually persists throughout life unless a specific treatment is given (spontaneous eradication is rare). *H. pylori* infects at least 50% of the world's human population(10) and poor socio-economic condition is regarded as the most important risk factor for acquisition of the infection(11). In developing countries most children reach adulthood being *H. pylori* positive (12-14).

Epidemiology

Prevalence of H. pylori infection in Indian Children

Poor socioeconomic status, overcrowding and unhygienic conditions contribute to the high prevalence of *H. pylori* infection in developing countries. Majority of infection is acquired in the first decade of life. The sero-prevalence studies from Hyderabad and Mumbai have shown that by 10 years of age more than 50% and by 20 years more than 80% of population is infected with *H. pylori*(13,14). Another study from Bangalore(15) has detected *H. pylori* infection in 82% of 50 children (6 to 18 years of age) by 13C urea breath test. The studies among adults have also shown a high prevalence of *H. pylori* (78%)(16,17). On the other hand hospital based studies have shown a slightly different figure. A study from Delhi in 258 patients admitted for non-gastroenterological disorders has shown the seroprevalence of 52% by 20 years of age and peak prevalence of 68% at 30-39 year of age(18). Another hospital based study on 400 patients (0 to 39 years of age) from Hyderabad, has shown the *H. pylori* positivity by PCR in saliva in 40% children by 10 years of age and this figure went up to 71% by 29 years of age(19). Most of these studies are in subjects of low socioeconomic status. A study, on subjects of high socioeconomic status of Chennai, has shown a much lower overall seroprevalence (49.4%). Seroprevalence increased with increasing age, ranging from 21% in the 12-20 years age group to 76% in the >70 years group. This pattern is like that of a developed country where seroprevalence increases with increasing age(20).

Environmental Factors

The major risk factor for *H. pylori* infection is the socioeconomic status of the family during childhood, as reflected in the number of persons in a household (person to person transmission), sharing of bed, sanitation and personal hygiene (fecal-oral transmission). Over the years, as the socioeconomic status has improved in developed countries, the prevalence of *H. pylori* in younger generations has declined(21). The age related apparent increase in the prevalence (higher in the older generation and lower in younger generation) in developed countries

could best be explained by the "birth cohort effect." As the organism persists almost throughout life, those who were born at the time of relatively poorer socioeconomic status have higher prevalence of *H. pylori* than those who were born recently with a better socioeconomic status ("birth cohort effect"). However this "birth cohort" phenomena is not seen in developing countries like India as the improvement of socioeconomic and sanitary conditions is much slower. In India, the prevalence of *H. pylori* is similar in children and in adults as there is no "birth cohort effect". Previously, it was believed that there is a very high re-infection rate in developing countries (almost 20% per year) as the environment (overcrowding, unhygienic surroundings) is conducive for it(22) and this may be an important factor for persistence of infection. However, a recent study from Mumbai has clearly shown that re-infection rate in adults after eradication is very low (2.4%) in India(23). A study in children from Germany has also shown a very low re-infection rate (2.3% per person per year) after eradication of *H. pylori* with triple drug(24). We need to understand the difference between recrudescence of uneradicated organism from reinfection. Previous studies, in which re-infection rate was shown to be very high, have either used less effective regimen (two drugs; amoxicillin and tinidazole)(25) or have shown ulcer recurrence rather than *H. pylori* re-infection(26). *H. pylori* clearance (absence of the organism at the end of therapy) and *H. pylori* eradication (absence of the organism after 4 weeks of completion of therapy) are the two main determinants of re-infection. If we take *H. pylori* clearance rather eradication as the evidence for efficacy of drugs then we are going to get a higher re-infection rate, if drugs are not potent. With the availability of more potent anti *H. pylori* regimen with very high eradication rate, chances of recrudescence of un-eradicated infection have almost disappeared.

Transmission of Infection

Infants are rarely infected in the developed world due to passively transferred immunity from the mother. However, in developing countries, like other enteric infections, *H. pylori* is common in infants also. In a study from Bangladesh, *H. pylori* infection has been shown in 46% of 90 infants studied(27).

H. pylori transmission is primarily “person-to-person” via fecal-oral, gastric-oral or oral-oral routes. Children acquire infection mainly through feco-oral route as *H. pylori* has been cultured from the stool of infected children(28). Gastric-oral route of transmission has also been recognized, as regurgitation and vomiting are common in children. Other modes of transmission in children are contaminated water and oral-oral route (by kissing and feeding of pre-masticated food).

Virulence Factors

Virulence factors help the organism to establish itself in the gastric mucosa and to produce disease in the host. Virulence factors of *H. pylori* may be divided into two groups; colonization factors (flagella, urease enzyme, and adherence factors) and factors responsible for tissue injury (lipopolysaccharide, leucocyte recruitment and activating factors, vacuolating cytotoxin or Vac A and cytotoxin-associated antigen or Cag A). The colonization factors not only help the organism to establish itself in the stomach but also help it to persist. With the help of flagella the organism move fast from the lumen of the stomach, where pH is low, through the mucus layer to an area where pH is neutral to permit optimal growth. The organism stays on the surface of the epithelium, under the mucus layer and never invades the mucosa. The enzyme urease makes the immediate environment alkaline by converting urea to ammonia. Adherence factors help the organism to bind to specific receptor on the surface of the gastric epithelium.

However, in addition to host factors, the virulence of the organism plays an important role. Lipopolysaccharides possess endotoxic properties (basically endotoxins) and stimulate the release of cytokines. *H. pylori* elaborates a number of soluble surface proteins like leukocyte recruitment and activating factors with chemotactic properties to recruit and activate monocytes and neutrophils. Vacuolating cytotoxin (Vac A) gene is present in all strains of *H. pylori* but only about half of them express the mature toxin(29). The Vac A gene has two families of alleles; the middle region (m1, m2) and the signal sequence (s1a, s1b, s2). Strains with the s2m2 genotype produce little or no toxin, whereas s1m1 is strongly associated with toxin

production and the presence of Cag A. A study by Singh, *et al.*(7) from Lucknow has shown that the children with upper abdominal pain have more frequent association with *H. pylori* strains with s1m1 alleles compared to the children without pain abdomen. It has been shown that the presence of Cag A is associated with more severe inflammatory tissue injury and consequently more *H. pylori* related disease than in asymptomatic gastritis(30). Initially it was suggested that Cag A positive *H. pylori* was associated with peptic ulcer disease and with more severe inflammation. However, recent studies in children have shown that Cag A or Vac A status does not determine the outcome of *H. pylori* infection(31,32).

H. pylori and Disease

H. pylori is etiologically associated with chronic active gastritis, duodenal ulcer, gastric ulcer, primary gastric B-cell lymphoma or mucosal associated lymphoid type lymphoma (MALT lymphoma) and gastric adenocarcinoma. Fortunately other than chronic gastritis, which is an asymptomatic condition, other diseases are infrequently seen in children and that is why most children infected with *H. pylori* are asymptomatic. At present there is no evidence to suggest a link between *H. pylori* gastritis and pain abdomen in the absence of ulcer disease. Therefore recurrent abdominal pain (RAP) cases should not be investigated for *H. pylori*. However, young adults are at risk of having *H. pylori* associated duodenal ulcer. Besides virulence of the organism, the host genetics and environmental factors (like diet, alcohol, smoking, *etc.*) play an important role in the pathogenesis of peptic ulcer and gastric cancer and this can explain why *H. pylori* infection in childhood produces diseases in adulthood(33). Recently, it has been shown that the host genetic factors [interleukin (IL1B) gene polymorphism, blood group ‘O’ *etc.*] determine the clinical outcome of *H. pylori* infection. A study from Calcutta has shown that the IL1B polymorphism is strongly associated with *H. pylori* related duodenal ulcer(34).

Studies from Italy, Germany and USA have shown that *H. pylori* infection is associated with growth delay especially in older children(35-37). However, it is not yet clear whether the difference in

anthropometry between *H. pylori* infected and non-infected children is solely due to *H. pylori* infection or the socioeconomic and ethnic factors also contribute to it. We need more information, especially from developing countries where *H. pylori* infection is rampant in children, before accepting that *H. pylori* causes growth retardation.

Iron Deficiency Anemia and H. pylori Infection

There is some suggestion that *H. pylori* causes iron deficiency anemia (IDA) especially in adolescent girls without producing any hemorrhagic lesions in the stomach or duodenum. Kostaki, *et al.* (38) from Greece first time reported that IDA in 3 children improved only after *H. pylori* eradication. Subsequently a report from Korea (39) on 937 children has shown that *H. pylori* infection was more common in children with IDA (35.5%) than in children without IDA (19.4%). A recent report from Turkey (40) on 140 children (6 to 16 years) has shown that iron deficiency (ID) and iron deficiency anemia (IDA) improved completely after *H. pylori* eradication without any iron supplementation. The postulated mechanisms for IDA in *H. pylori* infection are: poor absorption of iron due to low gastric acid secretion, poor dietary intake and consumption of iron by the bacteria itself.

Recurrent Abdominal Pain and *H. pylori*

The association of recurrent abdominal pain (RAP) and *H. pylori* is still debatable. There are evidences for and against this association. Firstly if

this association is true then *H. pylori* should be seen more frequently in RAP cases than in controls. *Table II* has shown that different studies from India and elsewhere have shown that there is no significant difference of *H. pylori* prevalence between RAP and controls. Moreover a study on 945 children from Germany (41) and 695 children from Sweden (42) have shown that there is no positive association between *H. pylori* status and the occurrence of pain abdomen, in fact there was an inverse association of *H. pylori* positivity and pain abdomen. However, a study on 240 children from Lucknow (4) has shown that the prevalence of *H. pylori* in upper abdominal pain (not RAP) cases is significantly higher than controls (53% vs 28%, $P < 0.001$).

Secondly, if this association is true then after eradication of *H. pylori* symptoms should disappear and with relapse, symptoms should reappear. Most of the studies from India (*Table I*) have shown that symptoms disappeared with eradication of *H. pylori* but none of these studies have given a follow up information. As we know that a substantial proportion (30% to 40%) of cases with functional disorders shows a placebo response with any form of therapy. None of these studies have compared drugs with placebo. So we cannot say for sure how much is true response and how much is placebo response. Oderda, *et al.* (43) have treated *H. pylori* gastritis in children with RAP and showed that symptoms resolved in the majority after eradication but recurred only in 13% of children while *H. pylori*

TABLE I—Association of Recurrent Abdominal Pain (RAP) and *H. pylori*

Study	Number of children	<i>H. pylori</i> positivity		Response to treatment	Association
		RAP cases	Controls		
Heldenberg, <i>et al.</i> (57)	50	54%	No	85%	+
Kumar, <i>et al.</i> (3)	33	43%	No	83%	+
Das, <i>et al.</i> (6)	65	77%	No	83%	+
Biswal, <i>et al.</i> (5)	76	65%	No	Most	+
O'Donohoe, <i>et al.</i> (58)	640	9.9%	18.2%	Not treated	Negative
Chong, <i>et al.</i> (59)	456	17%	10%	Not treated	+/- ($p < 0.05$)
Bansal, <i>et al.</i> (8)	57	23%	19%	Not treated	Negative
Yoshida, <i>et al.</i> (56)	47	30%	27%	Not treated	Negative

NS = not significant.

gastritis recurred in 73% of cases. In a recent study from Germany, Bode, *et al.*(44) have done a population based cross-sectional study on 1221 children and showed that RAP was associated with single parents, family history of non-ulcer dyspepsia but not with *H. pylori*. Similarly, Ashorn, *et al.*(45) in a double blind randomized placebo controlled trial on symptomatic response of *H. pylori* eradication in 20 children with RAP have shown that bacterial eradication and healing of gastric inflammation does not lead to symptomatic relief of chronic abdominal pain in children. A meta-analysis(46) of 45 series has shown that *H. pylori* is not associated with RAP. Considering every thing, European Pediatric Task Force on *H. pylori*(47,48) has suggested that to date there is no evidence demonstrating a link between *H. pylori* associated gastritis and abdominal pain except in those rare cases in which gastric or duodenal ulcer disease is present. Therefore, screening for *H. pylori* infection should not be performed routinely even in children with upper gastrointestinal symptoms, including abdominal pain. The Canadian Helicobacter Study Group(49) in their recent report on consensus conference on *H. pylori* has further substantiated this view.

Diagnosis

There are both invasive (requires endoscopy) and non-invasive tests for diagnosing *H. pylori* infection (Table II)(22). Invasive tests like rapid urease test (RUT), histopathology and culture of

gastric biopsy, are used for the diagnosis. While non-invasive tests like urea breath test and stool antigen detection are used to check for eradication of infection after treatment. Serum serology is mainly used for epidemiological purpose. As the serology persists for a long period after the eradication of the organism, it cannot be used to check eradication and for the same reason serology does not give an idea whether active infection is there or not. Among the non-invasive tests, the serology is unreliable in young children as antibody production is low in them. Similarly, the 13 C urea breath test is difficult to perform in <5 yrs age group. So far, "Gold standard" for the diagnosis of *H. pylori* is culture of gastric biopsy. However, positive rapid urease test (RUT) in gastric biopsy with histopathology showing *H. pylori*, is also accepted as an alternative to culture for the diagnosis of *H. pylori*. To check eradication (four weeks after therapy), 13C urea breath test is the best (UBT). Recently, it has been shown that the stool ELISA test for *H. pylori* antigen (HpSA) is also a good non-invasive test to check for eradication(50,51). In pediatric practice, a non-invasive test based on body secretions instead of blood is always a desirable choice. In this respect, the saliva serology for *H. pylori* is an ideal test in children. However, after the initial enthusiasm, a number of studies have shown inconsistent results with less optimum sensitivity and specificity(52, 53). Moreover, like any other serological test, it does not differentiate an active from the past infection. In rapid urease test (RUT), gastric biopsy is inoculated in a colorless urea-rich solution/media with a pH

TABLE II—Sensitivity and Specificity of Various Tests Used in the Diagnosis of *H. pylori*

Tests	Sensitivity (%)	Specificity (%)
<i>Non-invasive</i>		
Serum serology (IgG)	95	85
Saliva serology (IgG)	90	85
13 C urea breath test	95-98	95-98
Stool antigen (HpSA)	88-95	95-98
<i>Invasive tests requiring endoscopy</i>		
Rapid urease test (RUT)	90-95	98
Histology with special stain (Warthin-Starry silver stain)	98	98
Culture	90-95	100
PCR	95	95

sensitive dye. If urease is present in the gastric mucosal biopsy, it catalyzes the hydrolysis of urea into ammonia and carbon dioxide. The resultant increase in pH from ammonia generation changes the color of the indicator. Result of RUT is available in a few minutes time (5 to 30 minutes for in-house RUT) but commercial test (like CLO test) takes 2 to 24 hours to turn positive. In urea breath test, the urea labeled with ^{13}C (non-radioactive carbon atom) is ingested. If urease is present in the stomach, the labeled carbon dioxide will be split off and absorbed into the circulation, where its presence can be determined by analysis of expired breath (by mass spectrometer).

Whom to Investigate for *H. pylori* and How?

European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)(47,48) have recommended that only those children should be investigated whose abdominal symptoms are severe enough to suspect organic causes. Primary goal of testing is to diagnose the cause of clinical symptoms and not simply to detect the presence of *H. pylori* infection. Therefore endoscopy is the preferred method of investigation. There is no role of non-invasive tests in the initial evaluation. However, nobody has addressed the problem of developing countries, where profile of *H. pylori* infection in children seems to be different (more

often asymptomatic than symptomatic infection) and an invasive investigation facility like endoscopy is not easily available in pediatric practice. In a symptomatic patient, it is logical to follow the above mentioned guideline. However, asymptomatic or patient with unrelated symptoms should not be subjected to any form of investigation to detect *H. pylori*.

Whom to Treat and With What Drugs?

Anti *H. pylori* treatment should be given if there is endoscopic demonstration of duodenal ulcer or gastric ulcer in the presence of *H. pylori* infection. However, the decision to treat or not, in a patient with normal endoscopy and *H. pylori* positivity, is still a big dilemma. In general, it is not recommended to treat such patients. The anti *H. pylori* treatment option should be kept open in such a situation. Parents should be fully informed that eradication of *H. pylori* does not necessarily lead to any change of symptoms. They should also be informed of the potential adverse effects of drugs and should be given the option of refusing treatment(47,48). Drugs used to treat *H. pylori* are given in *Table III* and recommended eradication therapies in children are given in *Table IV*(47-49).

Confirmation of Eradication of the organism should be done 4 weeks after completion of treatment. Urea breath test or fecal antigen test is the preferred method in an asymptomatic subject,

TABLE III—Drugs Used in the Treatment of *H. pylori* Infection in Children

Drugs	Doses	Maximum doses	Common side effects
Amoxicillin	50 mg/kg/day	1 g bid	Diarrhea, rash, abdominal cramping
Clarithromycin	15 mg/kg/day	500 mg bid	Dyspepsia, nausea, abdominal cramping
Omeprazole	1 mg/kg/day	20 mg bid	No serious side effect
Metronidazole	20 mg/kg/day	500 mg bid	Dizziness, seizures, metallic taste
Bismuth subsalicylate	1 tablet (262 mg) qid or 15 mL (17.6 mg/mL) qid		Blacking discoloration of stools, discoloration of tongue, avoid in patients with influenza and (17.6 mg/mL) Chicken pox (risk of Reye syndrome)
Tetracycline	50 mg/kg/day	1g bid	GI irritation, phototoxic reactions, inhibition of fetal skeletal growth, staining of growing teeth (contraindicated in < 9 yrs of age)
Ranitidine bismuth citrate	1 tablet qid		Headache, confusion

qid: four times daily. bid: twice daily

Key Messages

- *H. pylori* infection is very common in Indian children especially in low socioeconomic status but most infected children remain asymptomatic throughout their childhood and only a small fraction develops peptic ulcer disease as young adults.
- There is no association of *H. pylori* and recurrent abdominal pain (RAP).
- We should not look for *H. pylori* to find a cause for non-specific abdominal symptoms.
- Endoscopy is the preferred method of investigation in children with upper digestive symptoms suggestive of organic disease after exclusion of other causes with non-invasive methods. However, limited availability of this test in children is a concern in India.
- No role of non-invasive method of *H. pylori* detection in the initial evaluation.
- Children with *H. pylori* related disease (ulcer, primary gastric B-cell lymphoma and atrophic gastritis with intestinal metaplasia) should be treated with triple drugs comprising of PPI and two antibiotics.
- In endoscopy negative *H. pylori* positive cases: treatment option should be kept open as there is no proven benefit and the risk of re-infection is always there.

TABLE IV–Recommended Eradication Therapies for *H. pylori* Disease in Children(47-49).

Choice of therapy	Drugs	Duration
First line: one proton pump inhibitor (PPI) and two antibiotics	1. Omeprazole+ amoxicillin+ clarithromycin 2. Omeprazole+ Amoxycillin + Metronidazole 3. Omeprazole+ Clarithromycin + Metronidazole	10 to 14 days
Second line (when there is no response to first line therapy)	1. Omeprazole+ Bismuth subsalicylate + Metronidazole +Amoxycillin or Tetracycline 2. Ranitidine bismuth citrate + Clarithromycin + Metronidazole	14 days

whereas repeat endoscopy is indicated if the patient is still symptomatic after therapy.

H. pylori Infection in children and Gastric Adenocarcinoma in Adults

World Health Organization has classified *H. pylori* as group I carcinogen for gastric carcinoma and an infected individual has two to eight times higher risk of gastric carcinoma than general population(54). Therefore the question arises as to whether we prevent acquisition or eradicate *H. pylori* in children to prevent gastric carcinoma in their adulthood? There are many points against the view and at present there is no justification in treating childhood *H. pylori* to prevent gastric carcinoma in adulthood(55).

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