Helicobacter pylori: Prevalence, Transmission, and Serum Pepsinogen II Concentrations in Children of a Poor Periurban Community in Bangladesh

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The aim of this study was to determine the age-specific prevalence of *Helicobacter pylori* infection in infants and children aged 1–99 months from a poor periurban community in Bangladesh. We also examined the frequency of infection among infants and their 53 immediate family members and evaluated the relationship between infection and fasting serum group II pepsinogen (pepsinogen II) concentration in 76 children. Sixty-one percent of 1–3 month-old infants tested positive for *H. pylori;* this rate declined steadily to 33% in children aged 10–15 months and then increased to 84% in children aged 5–8 years. The *H. pylori* infection rate was 2.5 times higher in children with illiterate mothers. No difference in infection rate was detected among the family contacts of infected vs. noninfected infants. *H. pylori*–infected children had significantly higher serum pepsinogen II concentrations than did noninfected children ($P < .001$). We conclude that infection with *H. pylori* is highly prevalent and occurs at an early age. An environmental factor or factors, rather than or in addition to intrafamilial spread of this infection, are important in poor communities of Bangladesh. The higher levels of serum pepsinogen II in *H. pylori*–positive children might indicate the presence of gastritis in such asymptomatic children.

Helicobacter pylori (*H. pylori*) has become the most frequent known cause of chronic gastritis [1–4] and plays an important role in the etiology of peptic ulcer disease [5–7], gastric cancer [8, 9], and nonulcerative dyspepsia [10] in man. Its role in gastritis [11, 12] and dyspepsia [13] in children has also received great attention.

While *H. pylori* infections occur worldwide, the great majority of information is from Australia, North America, and Europe. Knowledge of *H. pylori* infection is primarily derived from adults during medical checkups and endoscopic procedures, blood donors, asymptomatic health care workers, and industrial employees [14]. Little is known of the epidemiology of *H. pylori* infection in children, particularly those in developing countries.

The major reservoir of *H. pylori* is man, and the principal mode of transmission appears to be person-to-person. The precise route of transmission, however, remains obscure. Although current evidence suggests fecal-oral transmission [15], it is not fully known whether the organism spreads by close personal contact within families, particularly in communities with overcrowding and poor sanitation. Therefore, it is important to study the prevalence of *H. pylori* among family members to determine the potential for intrafamilial spread of the infection in developing countries.

Both pepsinogen I and II are present in the chief cells of the oxyntic glands of the gastric corpus mucosa, but only pepsinogen II is present in the gastric antrum. Colonization of the gastric mucosa by *H. pylori* is associated with histologically confirmed chronic gastritis. Increased serum pepsinogen concentrations appear to be related to the severity of gastritis in *H. pylori*–infected subjects. In adults [16, 17] and in children [18] with upper gastrointestinal disorders, a significant correlation between serum pepsinogen I and II concentrations, total inflammatory score, and *H. pylori* state has been observed. This suggests that both serum pepsinogen I and II concentrations might be useful markers for gastritis and have potential as an index of severity of gastritis in *H. pylori*–positive subjects. It has been further observed that in *H. pylori*–positive subjects, the increase in concentration of pepsinogen II was more pronounced than that of pepsinogen I [17]. Although, asymptomatic infection with *H. pylori* is highly prevalent and childhood acquisition is common in developing countries, information regarding the association of gastritis with *H. pylori* infection is very limited.

In the present study we assessed prevalence of *H. pylori* infection in infants and children and their family contacts in a poor periurban community in Bangladesh. Furthermore, in some children we measured the serum pepsinogen II level in order to evaluate the possibilty of an association with chronic gastritis.

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Patients and Methods

Description of the Study Area

The study was carried out at Nandipara, a periurban community 7 miles northeast of Dhaka city and populated by people of low socioeconomic status. A population of >3,000 with ~500 children <5 years of age live in a 2.5-square-mile area. Among the dwellers, 75% of the males are classified as day laborers, 20% as rickshaw pullers, and 5% as carpenters, servicemen, or small businessmen. Fifteen percent of the women are day laborers and 85% are housewives. Most of the families live in poorly constructed houses with mud or thatched walls and tin or thatched roofs. The average family size is five members. The slum has a municipal water supply for drinking and cooking, but for bathing, washing, and cleaning utensils, water from ponds and ditches is used. About 90% of the population uses hanging latrines, which are poorly constructed on bamboo poles near ponds or ditches, resulting in high fecal contamination of water. Most children defecate in open spaces. A clinic for minor illness has been run in Nandipara since 1986 by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B).

Study Population

Four hundred and sixty-nine infants and children of age 1–99 months, representing ~80% of the whole population of that age group, were included in the study. A majority of mothers of the children studied (79%) were illiterate. Of the 469 children, 90 were infants <1 year of age. About 4% of the children were severely malnourished (<60% weight for age of 50th percentile of National Centre for Health Statistics), and 46% were undernourished (weight for age, 61%–75%). Sixty-seven percent of the children were receiving breast milk.

Methods

Standardized and pretested questionnaires and forms were used to document baseline information and results of physical examinations including anthropometry. A ^{13}C-urea breath test (UBT) [19, 20], a noninvasive test to detect the presence of *H. pylori* infection in the stomach, was performed as described below.

Urea breath test. A breath sample was collected for baseline $^{13}CO_2$ determination in a Vacutainer tube (Becton Dickinson, Sparks, MD) following a 2-hour fast. The children <5 years of age then consumed 100 mL of whole milk, while the older children consumed 200 mL. Half an hour later, ^{13}C-urea (99% ^{13}C, Tracer Technologies, Boston) in 25 mL of water was administered orally in a dose of 30 mg for children <2 years of age, 40 mg for children 2–8 years of age, and 100 mg for those aged >8 years. Breath samples were again collected 30 minutes after administration of ^{13}C-urea. From children <5 years of age, samples were collected by means of a two-way pediatric mask with attached nonreturn inlet valve into a Vacutainer. From subjects >5 years old, samples were collected by their blowing through a pipe into a Vacutainer.

Samples were obtained in duplicate and transported to the University of Basel, Switzerland, for measurement of ^{13}C concentration of respiratory CO_2 by mass spectrometer. The excess over baseline value was expressed in parts per thousand (delta ‰). A breath test in which excess over baseline was at least 5.‰ at 30 minutes was regarded as positive for *H. pylori* infection.

To determine the frequency of infection in the family, UBTs were performed later among the family members of infants <1 year of age (eight UBT-positive and seven UBT-negative), who were selected randomly. Pretested questionnaires and forms were used to document baseline information of the family contacts as well.

Serum samples were also obtained for pepsinogen II determination from the first 76 children on the day of the UBT. Radioimmunoassay for serum pepsinogen II was performed with commercial kits (Pepsik-II, SORIN Biomedica, Salujjia, Italy) at the University of Basel.

Results

The proportion of infants and children with *H. pylori* infection, as detected by a positive ^{13}C-UBT, are presented in figure 1. Sixty-one percent of the very young infants, aged 1–3 months (n = 36), had a positive UBT, indicating *H. pylori*

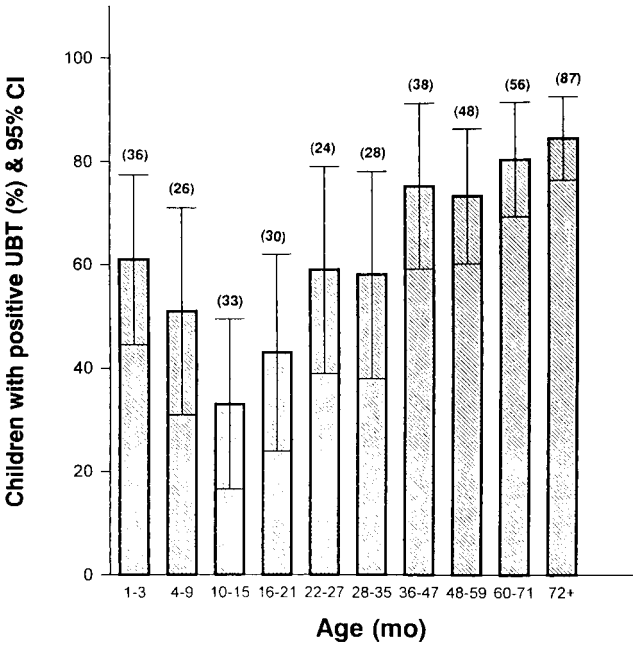

Figure 1. Age-specific prevalence of *H. pylori* infection, as detected by ^{13}C-urea breath test (UBT). The number of children in each age group is shown in parentheses on the top of each bar.

infection. The rate of infection steadily decreased with advancing age, to 33% in the 10–15-month age group. From the age of 16 months onward, the rate of positive UBTs steadily rose to 84% in children aged 6–9 years. The overall infection rate was 68% in the entire study population.

To evaluate the association of maternal education and the nutritional state with *H. pylori* infection, a logistic regression analysis was performed after adjustment for the several potential confounding factors, i.e., age, sex, crowding (persons living in the same room), low income, and use of antimicrobials during the 6 weeks preceding the study (table 1). In this model, the children of illiterate mothers had a nearly 2.5 times higher risk ($P < .001$) of being positive for *H. pylori.* However, malnutrition was not associated with the presence of *H. pylori* infection (OR, 1.23; $P = .34$). Age, sex, and crowding had no influence on infection rate.

To determine the prevalence of *H. pylori* infection in asymptomatic family contacts, UBTs were performed on the family members of eight infected and seven noninfected infants, selected randomly. We evaluated a total of 55 family members, of whom 33 and 22 were related to infected and noninfected infants, respectively. An equal prevalence of *H. pylori* infection was observed among the family members of both infected and noninfected infants ($\chi^2 = 1.9$; $P = .15$). No statistical difference was found in infection rate among the male contacts, female contacts, contacts <6 years of age, and parents of infected and noninfected infants (table 2).

Serum pepsinogen II levels were determined in a group of *H. pylori*–positive ($n = 57$) and *H. pylori*–negative ($n = 19$) children. Both these groups were comparable in respect to age and sex, nutritional status, and breast-feeding status (data not presented). The serum pepsinogen II concentrations were significantly higher in *H. pylori*–positive subjects than in *H. pylori*–negative individuals ($P = .002$) (figure 2).

Table 1. Association of nutritional status and maternal education level with *H. pylori* infection state (dependent variable) in children: logistic regression analysis.

Variable	Regression coefficient	SE	OR	*P* value
Undernourished (weight-for-age % of NCHS median; <75% = 1, other = 0)	0.218	0.221	1.2	.34
Maternal education (no formal education = 1, >1 y of schooling = 0)	0.880	0.256	2.5	.0006

NOTE. Adjusted for age categories of <3, 4–24, and <48 months; sex; persons living in same room; low income; use of antimicrobials during preceding 6 weeks; and lack of breastfeeding. NCHS = National Centre for Health Statistics.

Table 2. Prevalence of *H. pylori* infection among family contacts of infected and noninfected infants.

Variable	Contacts of infected infants	Contacts of noninfected infants
Total no. (infection rate)	33 (82%)	22 (91%)
No. of male contacts (infection rate)	17 (82%)	10 (100%)
No. of female contacts (infection rate)	15 (87%)	13 (77%)
All family members (including index cases) infected with *H. pylori*	50%	70%
Mothers infected (*n*)	7	6
Fathers infected (*n*)	6	7
Parents infected (*n*)	6	6
No. of children <6 y of age (excluding index case) infected	10	6
Infection rate (%)	70%	66%

NOTE. No statistical significance was found in differences.

Discussion

The purpose of this study was to determine the prevalence of *H. pylori* infection by means of a ^{13}C-UBT in asymptomatic infants and children in a poor community. An attempt was also made to examine the association between the prevalence of infection and nutritional status, socioeconomic status, age, and sex and to investigate whether the organism would spread by close personal contact within families. Serum pepsinogen II measurements were used as markers for presence of gastritis in this asymptomatic population.

This study demonstrates that the UBT can be applied even to infants as young as 1 month of age and gives a clearcut

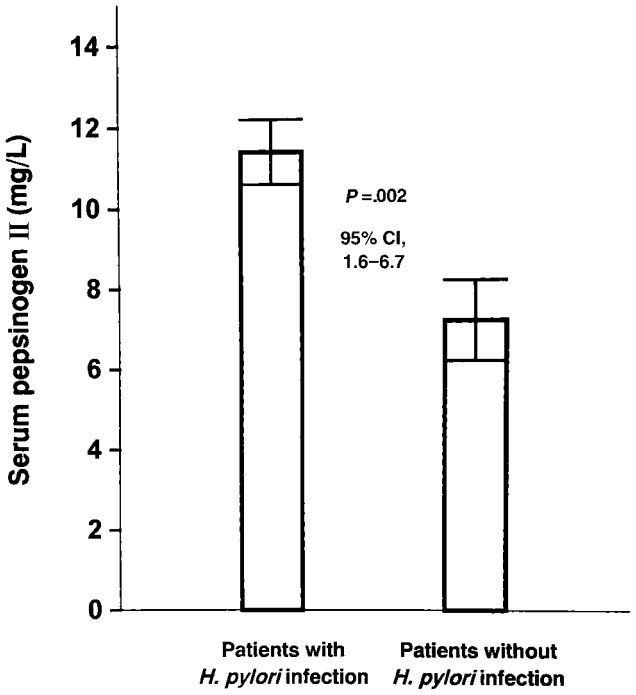

Figure 2. Serum pepsinogen II concentrations (mean ± SEM) in children with or without *H. pylori* infection.

result, i.e., the difference in the ratios ($^{13}CO_2/^{12}CO_2$) is either clearly positive or clearly negative. The only known urease-producing bacteria in the stomach is *H. pylori.* While some oral bacteria may be able to split urea, a breath sample taken at 30 minutes is likely to eliminate the possibility of oral bacteria yielding a positive UBT.

It should be pointed out that for infants this test has not yet been validated against the other ''gold standard,'' e.g., gastric biopsy, for obvious ethical reasons. Nevertheless, a high degree of sensitivity (95%–100%) and specificity (92%–100%) for this test in comparison with that of serology, culture, and histology has been reported with regard to children [21, 22], and it is considered a simple and reliable method for the diagnosis of gastric *H. pylori* colonization [23, 24]. There is now increasing consensus for use of this test as the ''gold standard'' in diagnosing active infection with *H. pylori* in persons of all ages, including young children [22–24].

We observed a high prevalence of *H. pylori* infection in infants aged 1–3 months; the infection rate then declined to 33% in the 10–15-months age group, and thereafter increased again to attain a high level of >80% by the age of 8 years. When 63 children with a history of taking antimicrobials during the 6 weeks preceding the UBT were included, the prevalence was similar to that in figure 1 (data not shown).

The prevalence observed in the present study is well above the rates for children living in India [25], Thailand [26], Ivory Coast and Algeria [27], Northern Nigeria [28], and the Gambia [29], in which 18%–60% of children were infected. The differences might be related to the characteristics of the population studied or to the laboratory methods used for detection of infection. It should be noted that our study population was derived from a densely populated area with overcrowding and poor environmental sanitation and water supply. Moreover, we used the UBT, which is the most sensitive and specific test to detect *H. pylori* infection [21, 22, 30]. Both these factors might be related to the higher prevalence of infection found in our study.

The reason for the decline in infection rate at 10–15 months of age is unclear but may be related to the body's defense mechanism in clearing the early infection. The subsequent rise in prevalence of infection beyond age 15 months may be related to the gastric mucosal damage caused by the initial infection, e.g., gastritis. This may lead to a facilitated and sustained infection with *H. pylori.* This finding of our study indicates that *H. pylori* infection is transient and self-limited in early infancy and is reacquired at a late age by children in developing countries. As this was a cross-sectional study demonstrating the point prevalence, caution is necessary in interpreting the results. However, the observations of early clearance and a subsequent rise in infection rate in late age are in accord with the results of a longitudinal study that involved a cohort of Peruvian infants and young children monitored for *H. pylori* status over a 2-year period with use of ^{13}C-UBT [31].

In this population, *H. pylori* infection was not apparently associated with a poor nutritional status. This finding is at variance with that reported by Sullivan et al. with regard to Gambian children [29]. In the Gambian study, no adjustments were made for possibly important confounders such as level of maternal education, which was an important risk factor in our study. Literate women tend to have a more protected lifestyle, provide better child care, and ensure a higher level of sanitation than do their illiterate counterparts. This finding is in accordance with that of Graham et al. [32], suggesting that this behavioral factor possibly has a protective role in the transmission of *H. pylori* infection.

An equally high prevalence of *H. pylori* infections among the parents and other family contacts of both infected and noninfected infants was noted in this study (table 2). The average prevalence rate in the family members of both groups of infants was about 85%. Although seroprevalence studies have demonstrated familial clustering [33–35] and clustering in institutions [26], suggesting person-to-person transmission, we did not observe this in our population. It should be noted that the population we studied lived in a densely populated area and had very poor environmental sanitation and water supply. It is likely that the contaminated environment, lack of proper sanitation, and lack of sufficient clean water may all explain the high prevalence of *H. pylori* in the adult population.

A high prevalence of *H. pylori* infection among the mothers of both infected and noninfected infants was also observed in this study (14/15; table 2), suggesting a role of environmental factors rather than a direct mother-to-infant mode of transmission. In contrast, a lower prevalence of *H. pylori* in neonates and young infants despite a high prevalence of *H. pylori* in their mothers has recently been reported [36]. This could indicate that mother-to-infant transmission accounts for little of the high prevalence of *H. pylori* infection in developing countries, where poor sanitation and environmental contamination are common.

It is also interesting to note that there were *H. pylori*–negative infants (index cases) in our study, even in families in which all other members were infected with the organism. This suggests that intrafamilial spread did not occur in this group of young infants. Transmission of *H. pylori* infection via the fecal-oral route or perhaps via contaminated water could therefore account for the high prevalence of this infection in these communities [37]. Recently, Thomas et al. [38] successfully isolated *H. pylori* from the feces of nine of 23 Gambian children. This lends further support to the premise that fecal-oral transmission of *H. pylori* can occur in a community with poor sanitation and environmental contamination.

In the present study we also analyzed the relationship between *H. pylori* infection and serum pepsinogen II concentration. The serum concentration of pepsinogen II was greater in children with *H. pylori* infection than in uninfected ones. Although endoscopy was not performed on these children, it has been shown before that patients with histologically proven gastritis have increased serum pepsinogen concentrations [39]. In fact, measurement of pepsinogen concentrations has been

proposed as a method for screening gastritis [16–18, 40]. Hyperpepsinogenemia as observed in *H. pylori*–infected children is therefore probably indicative of gastritis. Although the mechanisms by which *H. pylori* infection produces hyperpepsinogenemia remain unknown, it might be related to increased pepsinogen secretion or an increased leakage of pepsinogen into the circulation as a result of damage to chief cells and mucus neck cells.

In conclusion, our data suggest that *H. pylori* infection is highly prevalent in infants and children in Bangladesh and that acquisition of infection occurs in early infancy. Clustering of infection among family contacts could not be demonstrated in this study. Illiteracy of the mother, however, represented a risk factor. *H. pylori* infection is accompanied by increased serum pepsinogen II levels, suggesting the presence of gastritis even in asymptomatic children.

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