EDITORIALS

Helicobacter pylori Acquisition and Transmission: Where Does It All Begin?

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Since the discovery of *Helicobacter pylori* by Marshall and Warren almost 2 decades ago, overwhelming evidence has accumulated to confirm that *H. pylori* infection plays a significant role in the development of chronic active gastritis, peptic ulcer disease, and gastric adenocarcinoma. *H. pylori* infection is one of the most common bacterial infections of humankind. Over the past 15 years, epidemiologic studies have provided much information regarding this novel microorganism. It is now generally accepted that the human stomach is the primary reservoir for *H. pylori* and the prevalence of infection has been shown to increase with age in all populations studied across the globe. Significant progress has also been made in developing efficacious treatment regimens to eradicate the infection, and pharmacologic therapies have been used to effectively reduce the prevalence of peptic ulcer disease.

However, the mode of *H. pylori* transmission/acquisition remains ill-defined and the natural history of *H. pylori* infection and reinfection early in life remains poorly characterized. Although such information would prove interesting in rounding out the microbiology and pathogenicity of *H. pylori*, this information is of vital importance for the continued development of eradication and therapeutic strategies. Combination therapy consisting of 3 medications is still required to achieve acceptable *H. pylori* eradication rates. The treatment requires a great deal of compliance and can be cost prohibitive. Thus, such a treatment would be best served when administered to individuals when the risk of reinfection is minimal.[1] Similar considerations are important in the development of a prophylactic vaccine. If the risk of infection is negligible after a certain age, it would be impractical and even wasteful to administer such a vaccine to adults.

It has long been known that children from high-risk populations (those in which a high prevalence of *H. pylori* exists) acquire *H. pylori* infection early in life.[2,3] Thomas et al. screened 248 Gambian children, aged 3–45 months, for the presence of *H. pylori* infection, at intervals of 3 months over a 2-year period.[4] The age-related point prevalence, calculated from urea breath tests, increased from approximately 20% at 3 months to more than 80% at 30 months. Several other studies performed in developing countries from Africa and South America found the same was true regarding *H. pylori* infection in early life.[5] Additionally, previous studies have already shown that *H. pylori* infection clusters within families and that the acquisition of this infection is strongly linked to conditions associated with lower socioeconomic status during childhood, such as residential crowding.[6–8] Observations such as these support the hypothesis of person-to-person transmission of *H. pylori* infection. If close personal contact results in transmission of *H. pylori* infection, via either the oral-oral or fecal-oral route, it would be expected that the prevalence of infection would be found to be increased not only within families with *H. pylori*–infected members, but also as a result of close contact with infected children in day care centers. The study by Tindberg et al.[9] directly addresses the contribution of intrafamilial contact vs. close contact among children in the community in promoting person-to-person transmission of *H. pylori* infection. It provides some interesting insights into the source of *H. pylori* acquisition.

Tindberg et al.[9] examined the prevalence of *H. pylori* infection among 695 10–12-year-old school children around Stockholm, Sweden. *H. pylori* infection was identified by serum immunoglobulin G enzyme-linked immunosorbent assay and subsequently confirmed by Western blot and urea breath testing. Information on family size, antibiotic use, previous day care attendance, and national origin of the parents and child were obtained by questionnaire. The study population was significant in that virtually all children in this geographic region attend the public school system, insuring an accurate representation of the 10–12-year-old children within the district. By assigning each parent as originating from either a low, medium, or high prevalence area, an interesting pattern emerged. Although only 2% of the children born to parents originating from low prevalence areas were *H. pylori* positive, prevalence climbed to 33% and 55% when at least 1 parent originated from a medium or high prevalence area, respectively. The data clearly indicate a child's likelihood of *H. pylori* infection

is more closely associated with the origin and socioeconomic status of the mother over the father as evidenced by an odds ratio of 71.

Further analysis revealed that the prevalence of *H. pylori* infection among infected classmates was in no way determinative of the likelihood of being infected. Children born in Sweden to parents also born in low prevalence areas were examined. Those attending school with a seroprevalence of 30% were no more likely to be infected than children attending school with a seroprevalence of <10% (odds ratio, 1.1). These findings are consistent with the many previous studies documenting the low level of *H. pylori* acquisition in children over 5 years old, regardless of environment and family status. The present report and previous studies all support the widely held belief that infection with *H. pylori* most likely occurs in children less than 5 years old.

Perhaps the most intriguing piece of information obtained in this study, and one that supports their conclusion regarding the importance of intrafamilial association over extraneous child-to-child contact for *H. pylori* transmission, comes from an analysis of the day care history of these children. Almost 90% of the children assessed in this study had attended day care, yet no increased risk for *H. pylori* infection was observed compared with children that had received their care exclusively at home. These results are informative because day care is often provided to infants and children still believed to be within the window of vulnerability to *H. pylori* acquisition. More information as to the age during which day care was received, the duration, and the seroprevalence of the other children would be helpful in drawing a firm conclusion. But the data presented here do indicate that acquisition most likely occurs within the family.

Unfortunately, Tindberg et al.[9] studied a cohort of 10–12-year-old children and did not specifically evaluate the acquisition of *H. pylori* in the first years of life. *Helicobacter pylori*, like most enteric infections, is acquired during childhood. There have been a few recent studies that address the acquisition of *H. pylori* during the first few years of life. Guelrud et al.[10] assessed the prevalence of *H. pylori* in a group of neonates and young infants from a lower socioeconomic background. Antral biopsy specimens were obtained from 20 consecutive neonates and infants under the age of 2 months who were undergoing endoscopic retrograde cholangiopancreatography (ERCP) for an evaluation of neonatal cholestasis. Unlike the study by Tindberg et al. in which the actual *H. pylori* status of the mothers was not determined, in Guelrud et al.'s study, on the same day that ERCP examination of the child was conducted, the mother also underwent upper endoscopy. Antral specimens were obtained and the presence of *H. pylori* was determined. One of the 12 infants was found to be infected with *H. pylori*. Despite the fact that only 1 of 20 children was infected with *H. pylori*, 19 of the 20 mothers were positive by the CLOtest and histopathological assessment, including the mother of the infant who tested positively for *H. pylori*. All children in the study were breast-feeding. Nine of the children were receiving complimentary formula in addition to breast-feedings, including the infant infected with *H. pylori*. Despite close contact between *H. pylori*–positive mothers and their children, an extremely low prevalence of *H. pylori* infection was found in the children studied. If the Tindberg hypothesis is correct, this study suggests that transmission from mother to child would have to occur after the age of weaning.

Goodman et al. evaluated just such an age group by studying the effects of the family composition on the *H. pylori* prevalence in children aged 2–9 years in a rural area of the Columbian Andes. They showed a clear gradient of effect seen in birth order.[11] When the investigators examined the effects of birth spacing, they showed that children born within 4 years of an older sibling were 4 times more likely to be infected with *H. pylori*. The odds of having *H. pylori* infection seems to increase almost steadily with the total number of 2–9-year-old siblings in the home. This effect seems to depend entirely on the number of older siblings in the age range. The investigators concluded that birth order, birth spacing, and the infectious status of siblings influenced the odds of acquiring *H. pylori* infection independently of the number of children in the home and suggests that the organism is most readily transmitted among the siblings who are close in age and more frequently from older to the younger ones. This is in contrast to the results of Tindberg et al., which show that the intrafamilial transmission from a parent, and more specifically from mother to child, is the most significant risk factor for the acquisition of *H. pylori* infection.

The present study by Tindberg et al. provides strong evidence that the risk of *H. pylori* acquisition by school-age children from extraneous child-to-child contact is low and provides compelling data to support the notion that transmission primarily occurs from mother to infant child. Future studies in this area will require an in-depth analysis of the parent-to-child and sibling-to-sibling transmission in children under the age of 5 years old. Such studies would go a long way in identifying the primary means of infection. Until the means of acquisition and transmission for *H. pylori* infection are better defined, we should be cognizant of the potential exposure

and increased risk of infection that results from close contact of young children with *H. pylori*–positive family members and take appropriate precautions.

THOMAS G. BLANCHARD
STEVEN J. CZINN
Department of Pediatrics
Rainbow Babies and Children's Hospital
Case Western Reserve University
Cleveland, Ohio

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Address requests for reprints to: Steven J. Czinn, M.D., 11100 Euclid Avenue, Cleveland, Ohio 44106. e-mail: sjc3@po.cwru.edu.

0016-5085/01/$35.00
doi:10.1053/gast.2001.26769

Morphogenesis and Maintenance of the Gastric Epithelium: A Role for Sonic Hedgehog?

See article on page 317.

The alimentary tract develops from the primitive gut tube of endoderm surrounded by mesoderm via a series of complex transitions mediated by reciprocal signaling between the endoderm and mesoderm.[1] In the mouse, patterning of the alimentary tube is completed early in gestation with differentiation of mesoderm into muscle, leading to the recognizable organs of esophagus, stomach, small intestine, cecum, and colon. In contrast, the epithelium remains undifferentiated until relatively late in gestation. The gastric endoderm undergoes cytodifferentiation with the formation of a monolayer with short infoldings or buds with mostly presumptive multipotent stem cell and gastric precursor cells. Cellular differentiation continues until postnatal day 28 with the formation of distinct epithelial cell lineages arranged in tubular structures called zymogenic units divided into 4 successive regions: pit, isthmus, neck, and base.[2–4] The pit contains the mucus secreting pit-cells, the isthmus is formed by a series of immature cell types, the neck contains mucus-secreting neck cells, and the base is populated by the pepsinogen-secreting zymogenic cells and prezymogenic cells. The acid-secreting parietal cells, as well as enteroendocrine and caveolated cells, are scattered throughout the 4 regions. The stem cells, located in the isthmus, give rise to precursor cells which migrate bidirectionally.[5] The precursor cells further differentiate into the cells which make up the zymogenic unit.[4,6] The gastric epithelium is further organized into zones along the cephalocaudal axis containing a squamous forestomach and glandular epithelium, which is then divided into a zymogenic zone, a mucoparietal zone, and a pure mucous zone.[6] The differentiated gastric epithelium comprises a complex system of cell types organized in a highly structured, continually renewing architecture. The molecular events that control the process of cellular fate and organization in the gastric glands have not been fully elucidated. The article by van den Brink et al.,[7] in this issue of GASTROENTEROLOGY, proposes sonic hedgehog (Shh) as a candidate polarizing signal in gastric