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Childhood *Helicobacter pylori* Infection and Growth Impairment in Developing Countries: A Vicious Cycle?

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**ABSTRACT**

We hypothesize that infection with the gastric pathogen *Helicobacter pylori* in children in developing countries is the initiator of a vicious cycle of events that result ultimately in malnutrition and growth impairment. Acute infection with *H pylori* is accompanied by hypochlorhydria, which facilitates the acquisition of other enteropathogens because of removal of the gastric acid barrier, which then results in diarrheal disease and iron-deficiency anemia. This is likely to occur most frequently in developing regions where the prevalence of *H pylori* infection is disproportionately high and multiple enteric coinfections are common. The consequent synergistic impact of diarrheal disease and micronutrient deficiency on growth and cognitive function in children has significant public health implications for socioeconomic development in these countries.
The acquisition of Helicobacter pylori infection occurs primarily in early childhood. Acute infection, at least in adults, results in a transient or extended period of hypochlorhydria. We hypothesize that this period represents a critical phase for pediatric cohorts in developing countries because, within this window, the individual becomes more susceptible to (1) acquiring other enteropathogenic infections, which results in diarrheal illness, and (2) developing iron-deficiency anemia (IDA). The combined impact of these extragastric manifestations of H pylori infection ultimately results in impaired childhood growth and cognitive function caused by the comorbidity associated with malnutrition, micronutrient deficiency, and diarrheal disease.

**Evidence for our hypothesis**

Since the discovery of H pylori by recent Nobel Laureates Marshall and Warren in 1982, the pathogen has been shown to be a causative agent of disease states of varying degrees of severity including chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Host genetics, host immune responses, and bacterial virulence factors contribute to the multifactorial nature of disease progression. Interleukin (IL)-1β is a potent suppressor of gastric acid secretion, and polymorphisms in the IL-1 gene cluster resulting in high IL-1β production are associated with hypochlorhydria with chronic H pylori infection. More severe disease is also associated with specific bacterial factors such as the cag pathogenicity island and carriage of specific alleles of the vacuolating cytotoxin.

Although the discovery of H pylori heralded a major reevaluation of the etiology of peptic ulcer disease and distal gastric cancer, the major global impact of H pylori infection may yet be largely unrecognized. In developing countries the incidence of H pylori infection in infancy is high and has been associated with malnutrition and growth faltering. Indeed, the incidence of H pylori infection in maldnourished children is greater than in adequately nourished subjects. Moreover, there is an inverse relationship between early H pylori colonization, infant malnutrition, and socioeconomic status. It is believed that the acquisition of H pylori in infancy/childhood in developing countries has a more severe impact on general health compared with developed countries. We believe that the acquisition of H pylori in childhood in developing countries is the initiator of a vicious cycle of events that makes an impact on childhood morbidity and mortality, as summarized in Fig 1.

First, the association between acute H pylori infection and transient hypochlorhydria in adults is well documented. Hypochlorhydria usually resolves within several months. Experimental infection of animals with gastric Helicobacter species also results in initial hypochlorhydria, which in gerbils was reversible by treatment with recombinant IL-1 receptor antagonist. It is interesting to note that animal models have shown that hypochlorhydria can promote fecal transmission of infection, an observation that may have implications for H pylori transmission among humans. However, although there is less direct evidence to support an association between acute H pylori infection and hypochlorhydria in pediatric cohorts, accumulating evidence indicates that H pylori–infected children also have impaired gastric acid secretion.

Second, hypochlorhydria increases susceptibility to enteric infections such as typhoid and nontyphoidal salmonellosis, cholera, giardiasis, and other infections. Other organisms (eg, Escherichia coli, Shigella flexneri) are less susceptible to gastric acid and can survive exposure to acidic pH. Evidence from case-controlled studies that examined the association between proton pump inhibitor–induced hypochlorhydria and increased relative risk of acquiring enteric infections including Clostridium difficile, Giardia, and Salmonella supports the view that a reduction in gastric acid secretion may result in the acquisition of infections, as reviewed elsewhere (see Table 1). Thus, H pylori–induced hypochlorhydria may predispose to enteric infections, particularly in regions of the developing world where enteric infections are endemic. Evidence from develop-
ing countries indicates that *H pylori* infection may increase the risk of acquisition of coinfection with other pathogens including *Vibrio cholerae*, *Salmonella typhi*, *Shigella*, and various parasites. The resultant diarrhea post-acute *H pylori* infection leads to malnutrition and growth retardation in children. The recent linking of enteric protozoal infections in developing countries with impaired cognitive function in children further emphasizes the importance of the vicious cycle initiated by *H pylori* on childhood morbidity and potential for socioeconomic impairment.

Another potential consequence of hypochlorhydria is IDA. IDA is a major public health issue, particularly in children, in developing countries where the prevalence in these regions exceeds 50%. In addition to poor nutritional sources of iron in many regions, absorption of bioavailable iron can be compromised if there are alterations to gastric acid secretion (eg, see ref 58). Acidic pH is essential for the efficient reduction and complexation of iron (and other micronutrients) before absorption.

A possible causal role for *H pylori* in the onset of IDA is supported by epidemiologic studies in adults and children. A combination of the (1) hypochlorhydria-associated *H pylori* infection and (2) direct competition between *H pylori* and the host for iron are the likely main contributors to IDA. In developing regions, the micronutrient deficiency and clinical sequelae would be further exacerbated by malnutrition and concurrent enteric infections. Manifestations of clinically advanced IDA include increased childhood mortality and susceptibility to disease, reduced growth, and cognitive function. However, the impact of *H pylori* on acquisition of diarrheal pathogens and pediatric growth in developing countries has not yet been evaluated rigorously. Studies in developed countries on the role of *H pylori* in diarrheal illness have yielded conflicting results compared with those in developing countries. This is perhaps not surprising, given the markedly contrasting exposure to diarrheal pathogens in developing countries. To date, few studies have focused on children during the first few years of life, which is when acute *H pylori* infection and associated hypochlorhydria occur.

**CONCLUSIONS**

A combination of micronutrient deficiency and coinfection with diarrhea-inducing enteropathogens acquired as a consequence of *H pylori*-induced hypochlorhydria is likely to have a profound impact on pediatric populations in developing countries where the prevalence of *H pylori* is high and reliable nutritional sources of bioavailable iron are low. Thus, prevention of *H pylori* infection could potentially have an important impact on diarrheal diseases in the developing world.

**TESTING THE HYPOTHESIS**

Whether the hypochlorhydria induced by acute *H pylori* infection in childhood is associated with an increase in enteric infections and diarrheal disease, IDA, and growth impairment remains an important unanswered question. The impact of *IL-1β* gene cluster polymorphisms on acute *H pylori* infection–related hypochlorhydria in pediatric populations is unknown. These factors require evaluation by a multicountry longitudinal observational prospective cohort study in developing countries to determine the impact of *H pylori* and other enteropathogen infections on the epidemiology of diarrheal disease, IDA, and childhood growth. As a causative agent of human disease, the global impact of *H pylori* on childhood morbidity in developing counties may far outweigh its role in causing peptic ulcer disease and gastric cancer.

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