Special Article

Epidemiology and Pathophysiology of *Helicobacter pylori* Infection in Children

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ABSTRACT

Helicobacter pylori is one of the commonest bacterial pathogens in human. The organism is associated with development of peptic ulcer diseases, lymphoproliferative disorders and gastric cancer. Residence in a developing country, poor socio-economic conditions and genetic predisposition are regarded as risk factors. Prevalence of infection is higher in developing countries and re-infection is higher among under five children. It is transmitted mainly through feco-oral route in developing countries and gastro-oral route in developed nations. Transmission of 'close-contact infection' depends on the degree of mixing and age-distribution between susceptible and infected individuals. Host and bacterial factors with interaction of environment contribute pathogenicity. *H. pylori* cytotoxin-associated geneA (cagA), vacuolating toxinA (vacA) and adherence factors to gastric epithelium have been linked to enhanced pathogenicity of the bacterium. Host genetic polymorphism of cytokines, related legends, receptors and enzymes influence *H. pylori* infection. **[Indian J Pediatr 2007; 74 (3) : 287-290]**
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Key words : *Helicobacter pylori; Epidemiology; Pathophysiology; Genetic factors; Children*

Helicobacter pylori is a small, highly motile, gram-negative bacillus. It is one of the commonest bacterial pathogens in human.[1] At least half of the world's populations are infected by *Helicobacter pylori*.[2] However, most of the infected people (>70%) are asymptomatic, whereas only <30% are symptomatic.[1] Half of the symptomatic patients develop peptic ulcer diseases, lymphoproliferative disorders or gastric cancer.[1] Again, some of the infected individuals develop duodenal ulcer whereas other develop gastric ulcer. Prevalence of infection is different in between developing and developed nations.[1,2,3] There is explosion of interest regarding such variability of this infection. In the present study understanding remains incomplete and many questions remain unanswered concerning such variability. Keeping this in mind, the review is written to update health personnel specially clinicians regarding some fundamental issues of epidemiology and pathophysiology of this alarming health problem.

Epidemiology

Human is the only known reservoir of *Helicobacter pylori*.[1] Other reservoirs that have been proposed include water, domestic cats and housefly.[4,5] The risk factors described for acquiring infection include residence in a developing country, poor socio-economic conditions, overcrowding, and an ethnic and genetic predisposition.[6] Prevalence of infection is higher in developing countries than that of developed nations (Fig. 1).[1] In developed countries, although overall prevalence of infection in young children is <10%, up to 50% of children living in poor socio-economic conditions are infected[7]. Up to 80% of children under age of 10 years are infected in developing countries.[7] Prevalence of infection in India is 22%, 56% and 87% in 0-4, 5-9 and 10-19 years age group respectively.[8] In

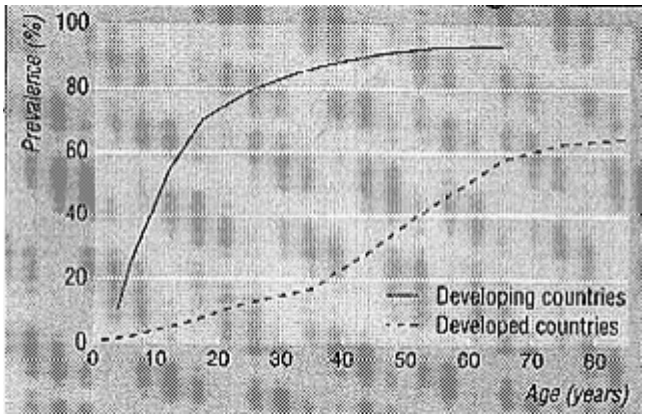

Fig. 1. Prevalence of *H. pylori* Infection by Age in Developing and Developed Countries.

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Bangladesh, such prevalence is 40% in infant[9] and 74% in 2-5 years age group[10] respectively. Important issue is that, throughout the developed countries, the infection is rare among children whereas in developing nation it is common in children.[11] It has been seen that there is no statistical difference of *H. pylori* infection between male and female children.[11] Studies in developing countries suggest that, until the last century, nearly all humans carried *H. pylori* or closely related bacteria in their stomachs, but with socio-economic development, fewer children are acquiring *H. pylori*.[12] Annual incidence of *Helicobacter pylori* infection is 0.3%- 0.7% in developed countries and 6-14% in developing nations.[1] Again, re-infection rate after treatment of *H. pylori* is higher in under five-age group of children.[7]

Helicobacter pylori infection is transmitted mainly through feco-oral route in developing countries and gastro-oral route in developed countries.[12,13] Transmission of 'close-contact infections' depend on the degree of mixing between susceptible and infected individuals, and also on the degree of crowding and age-distribution among those susceptible to infection and those are infected. Improvement in sanitary habits with increasing age may be an explanation for low re-infection rates in elderly peoples, but the change in degree of contact between family members as children grow up may also be important in reducing the exposure to infection.[7] Vector transmission also has been suggested, and it is biologically possible because the midgut of housefly has a favorable pH of 3.1 and may thus provide an etiological niche for *H. pylori* infection.[7]

Pathophysiology of *Helicobacter Pylori* Infection

Helicobacter pylori is almost always acquired in childhood, and if untreated infection is usually life-long.[2,7,14] Although prevalence of *H. pylori* infection is very high, only 15% of infected persons develop peptic ulcer disease.[15] Factors determining the subset of infected individuals developing disease compared with those remaining as *H. pylori* carriers remain unclear.[2] However host and bacterial factors contribute to differences in *H. pylori* pathogenicity.[2, 16, 17]

Helicobacter pylori virulence factors : Among microbial virulence factors identified so far, the *H. pylori* cytotoxin-associated geneA (cagA), its related pathogenicity island (cag PAI), vacuolating toxinA (vacA) and factors involved in adherence of *H. pylori* to gastric epithelial cells, have been linked to enhanced pathogenicity of the bacterium. The immunoreactive 120-145 kDa protein cagA is encoded by cagA of *H. pylori*.[2,17-,19] Some of the genes in the cagPAI region encode a type IV bacterial secretion apparatus, which can translocate cagA into host target cells. Phosphorylation of cagA may activate host signaling pathways and subsequently influence host cellular functions, including proliferation, apoptosis, cytokine release, and cell motility.[2,17-20] Individuals infected with $cagA^+$ strains are more likely to have gastroduodenal ulceration than those who are cagA.[-3]

About half of the *H. pylori* strains produce vacA, which induces epithelial cell vacuolation and cell death.[2, 16, 21, 22] VacA expression is determined by variations in the signal sequence (s1a, s1b, s1c, s2) and mid-region (m1, m2) of the vacA gene.[2, 16] Infection with s1a/m1 strains is associated with intense inflammation and duodenal ulceration.[3] The outer-membrane bound protein, BabA, is an adhesin of *H. pylori,* interacting with the blood-group antigen Lewis on gastric epithelial cells. The product of babA1 is identical to babA2 but cannot interact with Lewis.[2] *H. pylori* $babA2^+$strains are associated with an increased risk of peptic ulcers and distal gastric adenocarcinoma, whereas $babA2^-$ strains are more often associated with uncomplicated forms of gastritis.[2, 23] However, the same association was not seen in Japanese population.[3] Tripositive strains, which have $cagA^+$, vacAs1, $babA2^+$in single *H. pylori* species, further increase the risk of developing gastrodudenal ulcers and distal gastric cancer.[2, 23, 24] Individual harboring a $cagA^-$, vacAs2m2, and $babA2^-$ genotype rarely (<10%) showed intestinal metaplasia.[2, 23, 24]

Host factors : Host genetic factors might affect *H. pylori* colonization and development of diseases. Genetic polymorphism of the cytokines and other related legends, receptors and enzymes might influence *H. pylori* infection. The associations with the polymorphism of fucosyl transferase2 (FUT2 or secretor gene), FUT3 (Lewis gene), Interleukin 1A (IL-1A), IL-1B, IL-IRN, IL-8, IL-10, myeloperoxidase (MPO) and tumor necrosis factorA (TNF-A) and TNF-B have been reported. Polymorphism of other related genes, CD14, CXC chemokine receptor2 (CXC-R2), IL-IRI, nuclear factor KB2 (NF-KB2) and Tool like receptor4 (TLR4) are potential influencing factors of *H. pylori* infection.[25] Interlukin 1-B is a pro-inflammatory cytokine and a powerful inhibitor of gastric acid secretion. Host genetic factors that affect IL-1B may determine why some individuals infected with *H. pylori* develop gastric cancer or ulcers while others do not.[2]

Interactions between host, environment and H. pylori in the development of peptic ulcer diseases has been proposed (Fig. 2)[3]. A two-way interaction might exist between *H. pylori* and gastric acid that determines pattern of gastritis and hence clinical outcome. Infection in infancy is thought to lead pangastritis (low acid secretion status), whereas acuisition in latter childhood may lead to a predominantly antral gastritis only (high acid load).[15] Environmental factors such as smoking, malnutrition, high salt intake, vitamin deficiency and host factors are associated with low acid secretion status. These factors favor the colonization of *H. pylori* in the corpus with intense inflammation and further reduction in acid secretion. The resultant hypochlorhydria promotes *H. pylori* colonization, more intense corpus inflammation with subsequent development of gastric atrophy, gastric ulcer and cancer.[3] An intriguing finding for *H. pylori*-associated gastric ulcer is their predilection

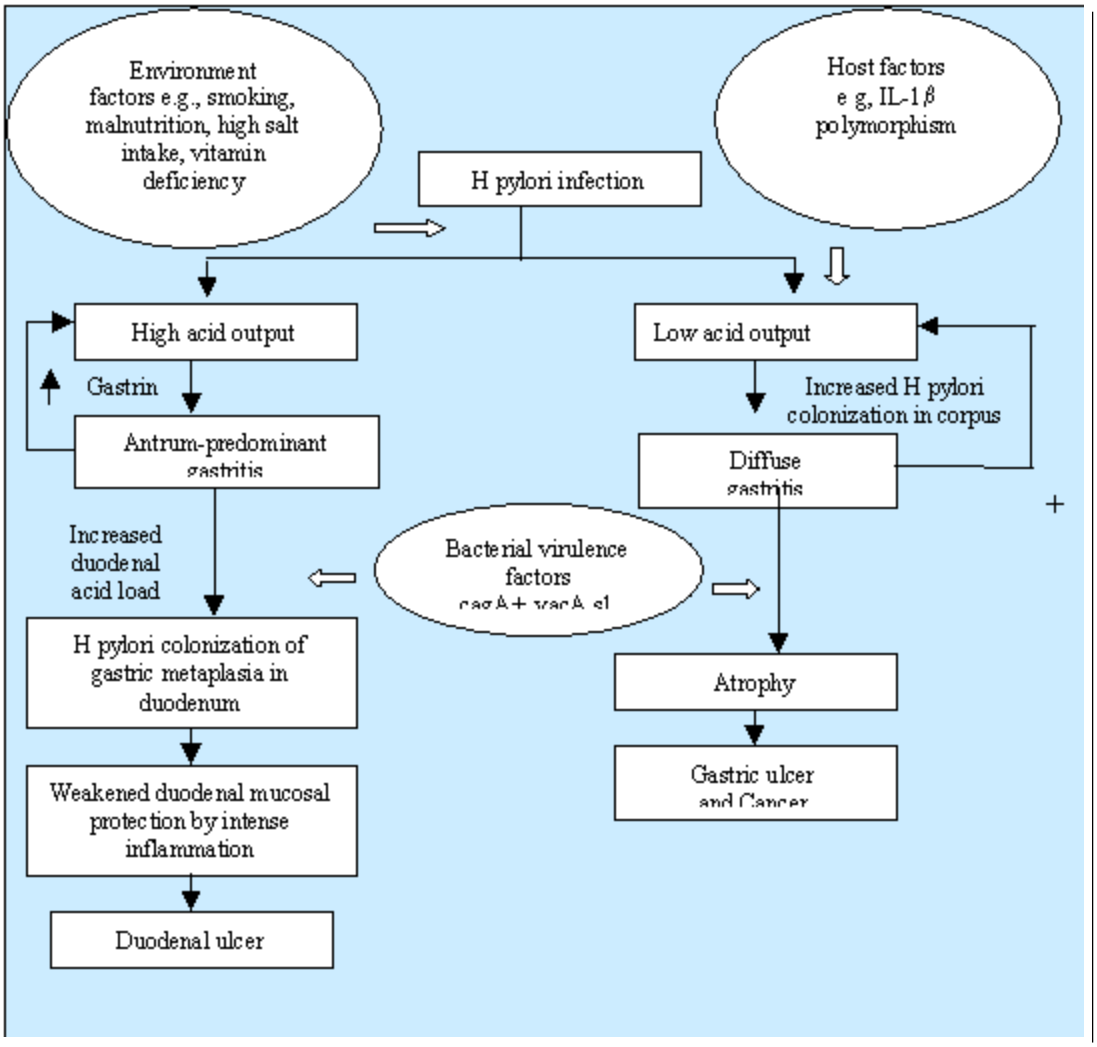

Fig. 2. Proposed Interaction Between Host, Environment and *H pylori* Infection in the Development of Gastric and Duodenal Ulcers

for the antrum-corpus junction *e.g.* 'transition zone' where there is dense colonization of *H. pylori* with maximum atrophy and gastric ulcer formation especially in the patients with low acid (HCL) output.[26]

In patients with high gastric output, which is determined by genetic, nutritional and other factors, the gastritis will be predominantly antrum in distribution. This pattern of gastritis is associated with hypergastrinaemia and increased acid production. Duodenal acid load leads to gastric metaplasia of duodenal bulb and *H. pylori* colonizes in this areas leading to duodenitis and eventually duodenal ulcer.[27,28] Patients with duodenal ulcer have impaired bicarbonate secretion in the proximal duodenum in response to acidification of the duodenum.[29] Unlike other pathophysiological defect, this impairment seems to be especially specific to duodenal ulcer patients and eradication of *H. pylori* will return duodenal bicarbonate secretion to normal in such children.[28]

CONCLUSIONS

Helicobacter pylori infection is one of the most common infections in human. Infection is mainly acquired in early childhood. Prevalence of such infection in pediatric age group is higher in developing countries. Re-infection chance is also more among children of such regions. Infection is transmitted mostly through feco-oral route in countries like ours. Only 15% infected children develop specific clinical conditions. Many questions remain unanswered regarding pathophysiology. But an interaction among host, environment and *H. pylori* has been proposed. These factors contribute whether the child will be asymptomatic or symptomatic. Again, these are related in development of nature of disease conditions. Identification of population at high risk of developing deleterious effect from *H. pylori* infection is ambitious. It remains a mainstream challenge for clinicians and basic

workers. However, if it is achieved, will make *H. pylori* related disease preventable through available effective treatment regimen.

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